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ХИМИЯ ҒЫЛЫМДАРЫ ИНСТИТУТЫ»
АКЦИОНЕРЛІК ҚОҒАМЫ

# ҚАЗАҚСТАННЫҢ ХИМИЯ ЖУРНАЛЫ

# ХИМИЧЕСКИЙ ЖУРНАЛ КАЗАХСТАНА

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# HYBRID MOLECULES BASED ON ALKALOIDS

***O.A. Nurkenov[1], S.D. Fazylov[1,2], G.K. Mukusheva*[2], Ye.V. Minayeva[2], I.V. Kulakov[3], Zh.S. Nurmaganbetov[1], A.S. Kishkentaeva[1], A.R. Zhasymbekova[2]***

*[1]LLC "Institute of Organic Synthesis and Coal Chemistry", Karagandy, Kazakhstan*
*[2]NLC Karaganda Buketov University, Karagandy, Kazakhstan*
*[3]FSAEI of HE "Tyumen State University", Russia*
*E-mail: mukusheva1977@list.ru*

**Abstract:** This review has been summarized the data on the synthesis of new hybrid derivatives based on alkaloid molecules. At the same time, there have been analyzed methods for obtaining hybrid structures containing fragments of natural compounds molecules in combination with other biologically active plant metabolites, as leading compounds for the development of new pharmacologically valuable agents, with the aim of creating new original drugs. The combination of pharmacophoric residues in one molecule, namely various aromatic and heterocyclic substituents in the nucleoside position of natural alkaloids, opens up new possibilities for both the subsequent chemical modification of the polyfunctional derivatives obtained and their new diverse biological activity. Effective methods of synthesis have been developed on the basis of directed transformations of these compounds (or their precursors). A wide range of pharmacological properties of combined compounds of these series with a combination of low toxicity is promising. Considering that the preparation of combined derivatives based on alkaloid molecules has been insufficiently studied, the targeted synthesis of new compounds is of interest both in terms of new medicinespreparation and the development of new methods of organic synthesis, as well as the molecules stereochemistry determination of a new series of compounds.

**Key words:** alkaloids, alkaloids derivatives, hybrid molecules, chemical modification, cytisine, anabasine, ephedrine.

## 1. Introduction

Molecular hybridization is one of the modern widely used approaches in the search for new and improvement of known medicines with a high level of action

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selectivity [1-4]. The combination in one molecule of two non-identical pharmacophores, covalently linked into one molecule, leads to a new compound that has the properties of both components. Hybrid molecules acting simultaneously on the receptor and on the enzyme can lead to powerful synergistic effects. Thus, the design of hybrid compounds and their use as medicines is a promising approach in the treatment of complex physiological disorders of the body.

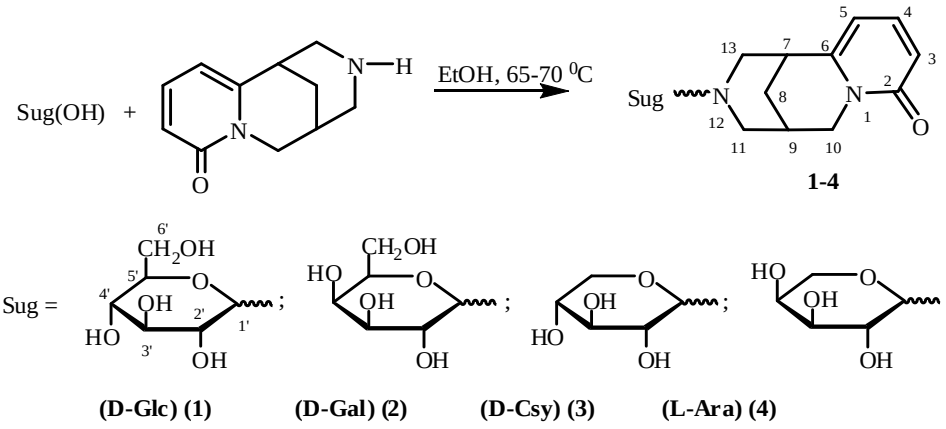
One of the promising directions of this strategy can be, in our opinion, the combination of heterocyclic systems of natural alkaloids and pharmacophore groups of other natural compoundsin one structure. The numerous data on the manifestation by alkaloids derivatives of a wide spectrum of bioactivity [5-7] are good prerequisites.Taking into account the valuable biological properties of alkaloids and their derivatives, the search for new ways of chemical modification of alkaloids is undoubtedly relevant, and the attention of researchers is attracted by the obtaining of more and more complexly constructed heterocyclic systems. Therefore, the introduction of alkaloids, fragments with biological activity into the molecules composition, is an urgent task and is of scientific and practical interest.

The methods development for the hybrid synthesis of various combined derivatives of the known alkaloids, namelycytisine, anabasine, lupinine, etc. is poorly studied and promising [7-10]. This approach allows us to expand the possible ways to search for new medicines.

**2. Results and discussion**

In this article, we present some of the results of many years of research on the chemical modification of quinolizidine and pyridine alkaloids with the participation of carbohydrate molecules, flavonoids, dihydroquercetin, fullerene and their modified derivatives. The combination of two physiological effects in a hybrid molecule is intended to produce a synergistic effect (increased efficacy) in the treatment of a disease or disorder. For example, the introduction of carbohydrate fragments into the structure of physiologically active substances not only increases their water solubility, but also significantly reduces toxicity, which makes it possible to recommend the method of glycosylation of a physiologically active compound at the glycosidic center of sugars as one of the possible ways to obtain low-toxic drugs [10-20]. It is also known that carbohydrates in the form of various derivatives are part of the cells of any living organism, playing here the role of a structural material, a supplier of energy, substrates and regulators of specific and biochemical processes. Carbohydrates, combining with nucleophilic acids, proteins and lipids, constitute high-molecular complexes that underlie subcellular structures and constitute the basis of living matter [19]. They are widely used in the treatment of cardiovascular diseases, used as antitumor, antimicrobial, and anticholinesterase agents [20].

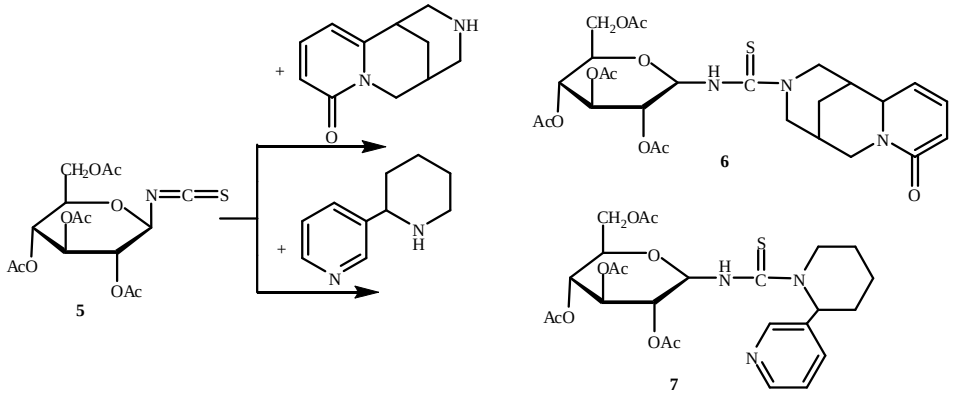
In this regard, it was of interest to obtain N-glycosylamines based on the alkaloid cytisine and some monosaccharides for the subsequent study of their biological properties. The synthesis of N-glycosylamines **1-4** was carried out by the well-known classical method proposed by V. Sorokin in [21]. The condensation of the cytisine molecule with the monosaccharides D-glucose, D-galactose, D-xylose, and L-arabinose was carried out in the medium of absolute ethyl alcohol (without the addition of a catalyst) **1-4**:



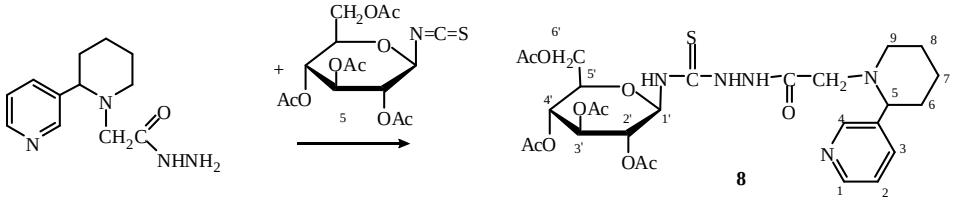

N-glycosylcytisines obtained **1-4** have good solubility in polar solvents and may be of interest as analogs of the respiratory analeptic “cytiton”, remedies for smoking cessation “lobesil”, “tabex”, since, undoubtedly, they will have much lower toxicity and prolongation actions due to their gradual hydrolysis in the body.

As is known, glycosylisothiocyanates are important intermediate synthons in the synthesis of various biologically active compounds [22]. The isothiocyanate method makes it possible to introduce a thioamide group into the structure of amines (alkaloids) and hydrazides with the formation of thioureas and thiosemicarbazides, which not only expands the boundaries of these compounds modification, but can also lead to the emergence of new types of bioactivity. Glycosylthioureas are usually obtained by the Fischer reaction, that is interaction of the corresponding amino compounds with glycosylisothiocyanate [22-24].

We carried out the interaction of 1-isothiocyano-1-deoxy-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose **5** with cytisine and anabasine [7, 8]. It was found that glycosylisothiocyanate **5** reacts quite easily with the indicated alkaloids in o-xylene solution at room temperature. The compounds synthesized **6, 7** have been obtained in 70-80% yields.

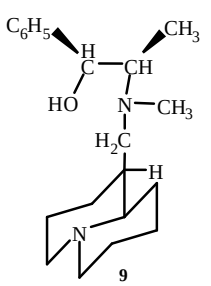


The addition of hydrazides to isothiocyanates is one of the convenient methods for the synthesis of thiosemicarbazides. It is known [25-27] that thiosemicarbazide derivatives have a wide range of biological actions, namely anticonvulsant, glypoglycemic, anti-inflammatory, and antibacterial ones. Therefore, it was of interest to synthesize a new thiosemicarbazide derivative **8** based on N-anabasinylacetic acid hydrazide. Thus, a thiosemicarbazidederivative **8** based on N-anabasinyl-acetic acid hydrazide was synthesized by the condensation of N-anabasinylacetic acid hydrazide with 1-deoxy-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl-iso-thiocyanate **5** in an alcohol solution at an equimolar ratio of the reagents used.



In [28], the results of hybrid synthesis of molecules combining fragments of two alkaloids in the structure are presented. The synthesized hybrid derivatives of *l*-ephedrine and *d*-pseudoephedrine with lupinine and epilupinine are of interest not only for studying their biological properties.They are also interesting as chiral catalysts in the formation of a new carbon-carbon bond in the production of chiral pheromones.

Bromolupinine was used as a synthonfor the synthesis of N-lupinan-*l*-ephedrine **9** and N-lupinan-*d*-pseudoephedrine **10**, and epilupinine bromide was used for N-epilupinan-*l*-ephedrine **11** and N-epilupinan-*d*-pseudoephedrine **12** synthesis. The reactions were carried out in a sealed ampoule in a metal container (bomb) filled with glycerol.



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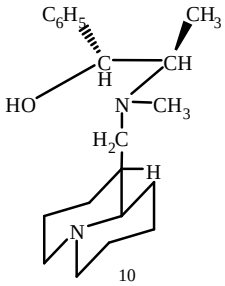

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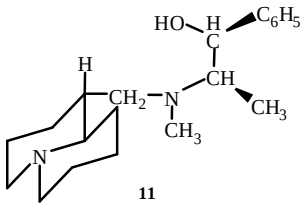

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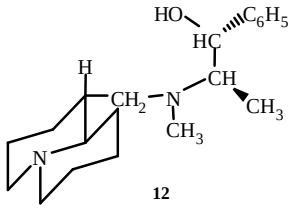
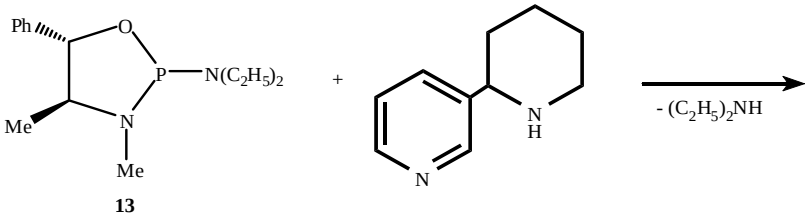
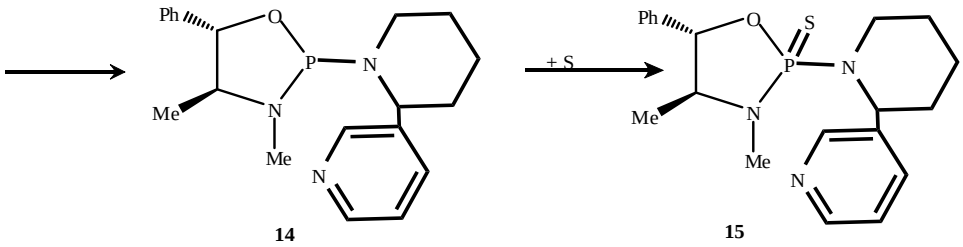


**12**

The authors of [29] studied a hybrid reaction of transamidation of d-pseudoephedrine cycloamidophosphite **13** with anabasine alkaloid. It was found that cycloamidophosphite **13** is an effective phosphorylating agent, the use of which makes it possible to introduce the oxazaphospholane cycle into the backbone of the anabasine alkaloid. Further, the cycloamidophosphite **14** obtained was modified by interaction with sulfur into a 2-thione-derivative of amidophosphate **15**.



**13**

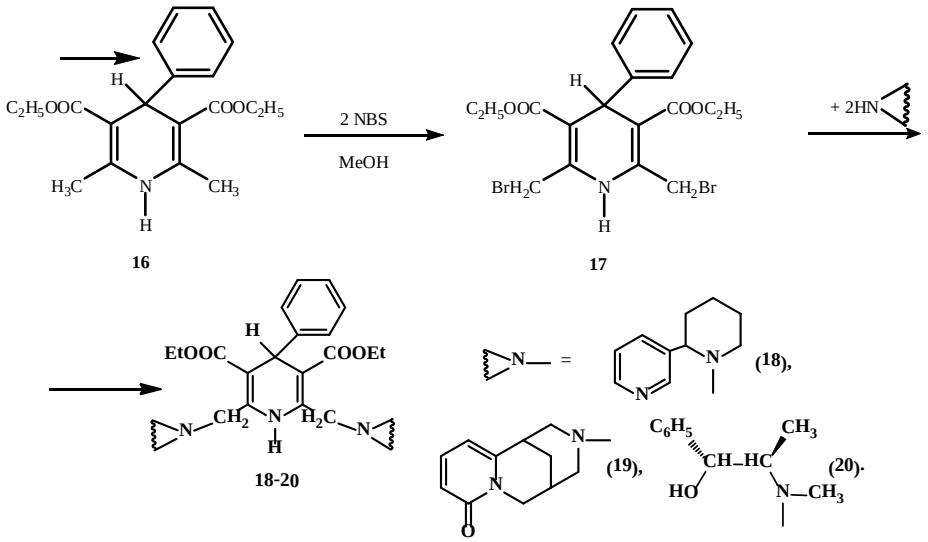


**14** **15**

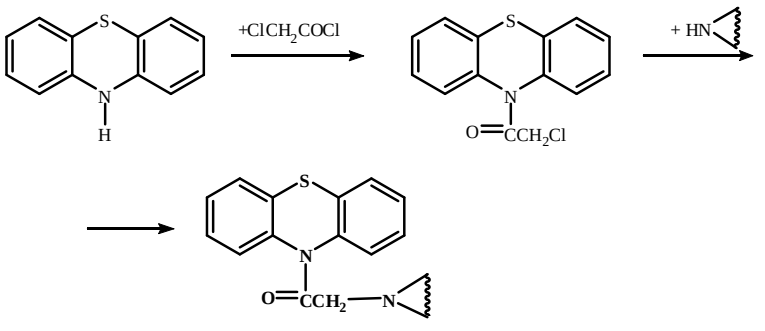
Recently, a new class of heterocyclic compounds with a basic 1,4-dihydropyridine base, possessing high antihypertensive and nootropic activity, has begun to be widely used in medical practice [30].

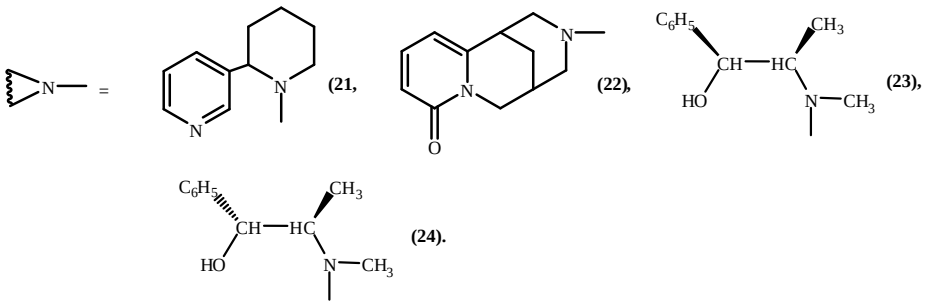
The Hantzsch method applied for the synthesis of symmetric 1,4-dihydropyridines has a wide variation of used practically available aliphatic, aromatic or heterocyclic aldehydes, various derivatives of acetoacetic ester and ammonia (or primary amines), which makes it very promising for further search for new biologically active compounds and their chemical modification.

In [31], the corresponding diethyl 4-(4-phenyl)-2,6-dimethyl-1,4-dihydropyridino-3,5-dicarboxylate **16**, which was used further for the subsequent reaction of halogenation and substitution,was synthesized by the Hantzsch method, in 60% yield by the three-component condensation of 2 moles of acetoacetic ester, benzaldehyde and 25% aqueous ammonia solution. Bromi-nationof compound **16** was carried out using a mild brominating agent, namely bromosuccinimide, at room temperature in methanol according to the method described in [32]. Using a double excess of bromosuccinimide, the corresponding dibromomethyl derivative was obtained **17**. The resulting dibromomethyl 1,4-dihydropyridine derivative **17** turned out to be quite reactive in the nucleophilic substitution reaction. Thus, the products of alkylation **18-20** were isolated in the interaction of a benzene solution of **14** with a double amount of alkaloids anabasine, cytisine, and d-pseudoephedrine. The reactions were carried out in the presence of an excess of triethylamine at room temperature and vigorous stirring during the day.



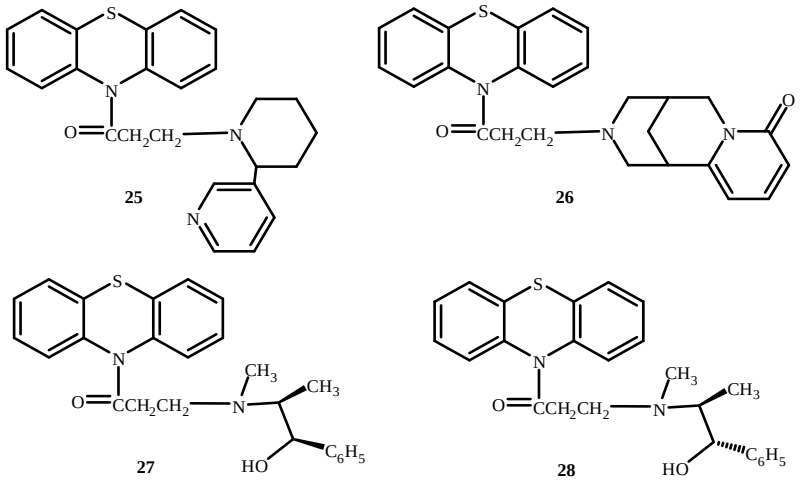

Phenothiazine with a condensed tricyclic system isone of the poorly studied objects in combination synthesis with alkaloids. It is widely studied in the synthesis of insecticidal and antihelminthic drugs [33]. In addition, phenothiazine itself, like many sulfur-containing derivatives, has very low toxicity for warm-blooded animals [34]. In [7,8,35], the authors synthesized previously unknown phenothiazine derivatives of cytisine, anabasine, *l*-ephedrine, and *d*-pseudoephedrine **21-24** alkaloids:



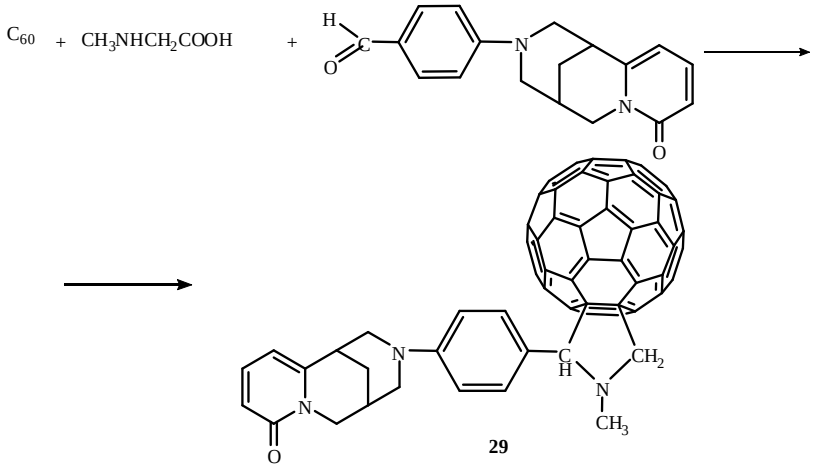




Alkylation of cytisine, anabasine, *l*-ephedrine, and *d*-pseudoephedrine alkaloids with 10-(2-chloroacetyl) phenothiazine was carried out in boiling toluene in the presence of triethylamine. Column chromatography and re-precipitation of hydrochlorides into the base were used to purify the target products.

In order to further study the structure-activity relationship, N-alkaloid-propionyl derivatives of phenothiazine were also obtained **25-28**, since 10-aminopropionyl derivatives of phenothiazine have high cholinergic and adrenolytic activity, antianginal and antiarrhythmic action [34].



A very new and interesting direction in the alkaloids hybrid synthesis is their fullerene derivatives. Fullerenes attract the attention of researchers by their potential for practical application in science, biology, and medicine, in semiconductor technology and nanoelectronics [36-38]. The main directions of obtaining new materials and biologically active compounds based on fullerenes are associated with their functionalization using various reagents. Analysis of the literature data shows that the synthesis of organic fullerene $C_{60}$ derivatives containingpharmacophore groups is of the greatest interest [39-43]. Fulleropyrrolidines obtained by the Prato reaction are the most widely studied in the fullerene chemistry. There is very little information in the scientific literature on the chemical modification of natural compounds with the participation of $C_{60}$ fullerene. In [44, 45], we described the synthesis of a new fullerene-containing derivative of the alkaloid cytisine **29**. The synthesis of a new fulleropyrrolidine compound with the participation of fullerene $C_{60}$ was carried out in a three-component medium with sarcosine and 4-cytisinobenzaldehyde in boiling toluene for 4 h according to the following scheme:



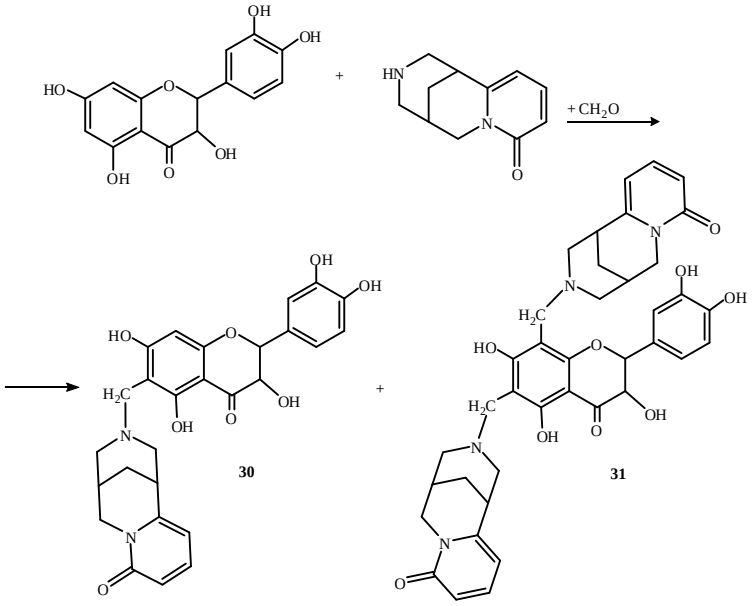

**29**

After the reaction, unreacted starting materials and the reaction product **29** were separated by column chromatography on $SiO_2$, eluting with toluene and then with pyridine. In this case, the starting unreacted fullerene $C_{60}$wasisolated, and then the target fulleropyrrolidine **29** was isolated with a yield of 38%.

A probable scheme for the formation of fulleropyrrolidine **29** was proposed as a 1,3-dipolar addition to fullerene $C_{60}$ through the intermediate formation of active azomethinylides: condensation of aromatic aldehyde with sarcosine occurs at the first stage of the reaction as a result of nucleophilic addition of the amino group of sarcosine to the carbonyl group of the aldehyde. Further, water is first eliminatedin the adductformed, and then decarboxylation occurs with the formation of azoylide, which nucleophilically attacks the fullerene core at the bond (6-6). As a result of the azoylideaddition to the bond (6-6) of the fullerene core, a pyrrolidine ring appears.

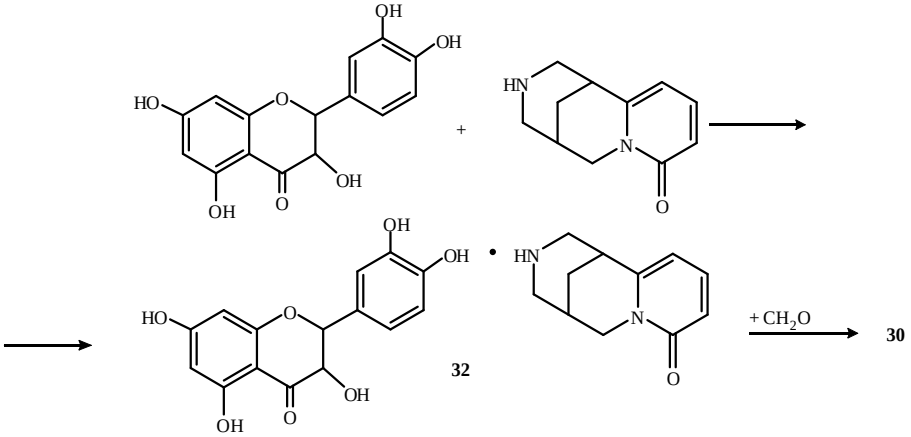
The synthesis of hybrid molecules, including fragments of natural compounds with the participation of flavonoids and alkaloids, can open the way to a wide range of new compounds with potential biological activity. Flavonoids represent a large group of natural compounds, among which dihydroquercetin (DHQ) and quercetin (Q) and their derivatives, possessing powerful antioxidant, hepatoprotective, antitumor, immunomodulating, and other properties, occupy a special place [46]. Interest in dihydroquercetin and quercetin is due to the fact that these flavonoids are actively used in the food industry and medicine. Both flavonoids belong to the group of phenolic compounds with antioxidant effects. In medical practice, dihydroquercetin and quercetin are used to treat radiation sickness, septic endocarditis, to prevent capillary lesions, etc. [47]. In recent years, quercetin has been found to be active against HIV-1 reverse transcriptase and integrase, as well as an inhibitory effect against the herpes virus [48]. The high biological activity and low toxicity of dihydroquercetin compounds make it possible to refer them to the group of leading compounds for chemical transformation in order to synthesize new hybrid polyfunctional pharmacologically active compounds.

N.V. Koshelevoy et al. [49] obtained a mixture of mono- and disubstituted derivatives **30** and **31** in a ratio of 2:1 (according to the HPLC method data), using the example of the interaction of DHQ, cytisine and formaldehyde according to the Mannich reaction in a molar ratio of 1: 1.4: 1.4 by adding a mixture of reagents to the substrate. Authors obtained a mixture of mono- and disubstituted DHQ derivatives in a 2:1 ratio with a two-fold excess of reagents and the reverse addition. It was shown that the formation of the disubstituted derivative **31** is associated with the higher basicity of the alkaloid cytisine.

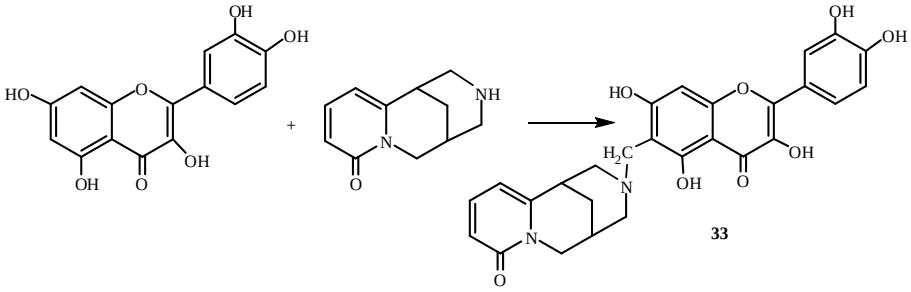


In order to simplify the direction of the reactionstudied, we introduced a significant change: dihydroquercetin was replaced by a complex with cytisine. Complex **32** was obtained by short-term contact of equimolecular amounts of the starting reagents and it spontaneously separates from the reaction mixture. According to its properties, the adduct is not a salt like ammonia derivatives formed due to the interaction of one of the phenolic hydroxyls of dihydroquercetin with the nitrogen atom of the cytisinealkaloid.

Complex **32** was reacted with formaldehyde at room temperature in 2-propanol. In this case, the expected reaction product was isolated in the form of an individual yellowish powder **30**.

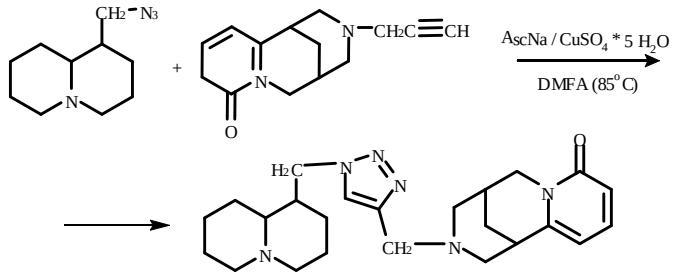



The presence of several hydroxyl groups, two aromatic rings and a pyrone ring in the quercetin molecule allows its chemical modification in order to obtain a number of new biologically active derivatives of interest for medicine. Thus, we were interested in the synthesis of an aminomethyl derivative of quercetin **33** based on the physiologically active alkaloid cytisine. The synthesis was carried out in a dioxane medium by adding an equimolar amount of a mixture of paraform and cytisine in dioxaneto quercetin.




Recently, 1,2,3-triazoles have been actively used as a linker fragment connecting two pharmacophores due to their exceptional pharmacokinetic characteristics: the ability to form hydrogen bonds and increase the solubility of

compounds, stability *in vivo* [50, 51]. The attractiveness of 1,2,3-triazoles is due to the versatility of their reactivity, as well as the practical use of derivatives of 1,2,3-triazoles as drugs, technical reagents and "building blocks" in supramolecular chemistry. It should be noted that the 1,2,3-triazole fragment has established itself as the most significant pharmacophore group; therefore, the modification of alkaloids by introducing such a substituent is one of the priority areas of organic and medicinal chemistry. In this regard, we have synthesized a new biologically active compound **34** containing simultaneously fragments of the alkaloids cytisine, lupinine and pharmacophoric 1,2,3-triazole. We have chosen an effective modern method of azide-alkyne cycloaddition catalyzed by copper compounds. N-propargylcytisine was used as an alkyne component of this cycloaddition reaction. The starting lupinineazide was obtained by the reaction of nucleophilic substitution with the azide ion of the corresponding mesylate of the lupinine derivative. The reaction of lupinineazide with N-propargylcytisine was carried out by heating (85°C) the reagents in DMF in the presence of $CuSO_4$*$5H_2O$ and sodium ascorbate. The combination of Cu (II) with sodium ascorbate provided regioselective formation of 1,2,3-triazole; in this case, sodium ascorbate acted as a reducing agent, excluding the homocombination product formation.




**34**

Thus, the material presented in this article testifies to the feasibility and prospects of searching for new hybrid biologically active compounds based on plant alkaloids.

Hybrid synthesis with the participation of natural alkaloids and fragments of various physiologically active compounds is a new promising scientific direction. Hybrid molecules acting simultaneously on the receptor and on the enzyme can lead to powerful synergistic effects. Hybrid synthesis medicines can be obtained by combining ligands belonging to completely different pharmacophores. Hybrid molecules can be obtained by combining two components with different activity (associative synthesis) or from a compound with a double action. The combination of two non-identical pharmacophores in one molecule leads to a new compound that has the properties of both components.

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## Information about authors:

Nurkenov Oralgazy Aktayevich – Doctor of chemical sciences, Professor; e-mail: nurkenov_oral@mail.ru; ORCID ID: https://orcid.org/0000-0003-1878-2787

Mukusheva Gulim Kenesbekovna (corresponding author) – Candidate of chemical sciences, Associated Professor; e-mail: mukusheva1977@list.ru; ORCID ID: https://orcid.org/0000-0001-6706-4816

Minayeva Yelena Viktorovna – Candidate of chemical sciences, e-mail: yelenaminayeva@yandex.ru; ORCID ID: https://orcid.org/0000-0001-9382-5965

Zhasymbekova Aigerym Rysbekovna – PhD student, e-mail: aigera-93-93@mail.ru; ORCID ID: https://orcid.org/0000-0003-1272-9096

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**Түйіндеме**

**АЛКАЛОИДТАРДЫҢ НЕГІЗІНДЕГІ ГИБРИДТІ МОЛЕКУЛАЛАР**

***О.А. Нүркенов[1], С.Д. Фазылов[1,2], Г.К. Мұқышева*[2], Е.В. Минаева[2], И.В. Кулаков[3], Ж.С. Нұрмағанбетов[1], А.С. Кішкентаева[1], А.Р. Жасымбекова [2]***

*[1]"Органикалық синтез және көмір химиясы институты" ЖШС, Қарағанды, Қазақстан*

*[2]«Академик Е.А. Бөкетов атындағы Қарағанды университеті» КЕАҚ, Қарағанды, Қазақстан*

*[3]«Тюмень мемлекеттік университеті» ФМА ЖОО, Ресей*

*E-mail: mukusheva1977@list.ru*

Ұсынылған шолуда алкалоид молекулаларына негізделген жаңа гибридті туындылардың синтезі туралы мәліметтер жинақталған. Бұл ретте жаңа бірегей дәрілік препараттарды жасау мақсатында жаңа фармакологиялық құнды агенттерді әзірлеу үшін көшбасшы қосылыстар ретінде басқа биологиялық белсенді өсімдік метаболиттері мен үйлесімде табиғи қосылыстар молекулаларының фрагменттері бар гибридті құрылымдарды алу әдістері талданған. Табиғи алкалоидтардың нуклеозидті жағдайындағы әр түрлі ароматты және гетероциклді алмастырғыштардың бір молекуладағы үйлесімі алынған полифункционалды туындыларды кейінгі химиялық модификациялаудың жаңа мүмкіндіктерін және олардың жаңа әр түрлі биологиялық белсенділігін ашады. Осы қосылыстардың бағытталған түрлендірулері негізінде синтездің тиімді әдістері әзірленді. Осы қатарда біріктірілген қосылыстарының фармакологиялық қасиеттерінің кең спектрі перспективалы болып табылады. Алкалоид молекулалары негізінде біріктірілген туындыларды алу жеткілікті зерттелмегенін ескере отырып, жаңа қосылыстардың бағытталған синтезі жаңа дәрілік заттарды алу тұрғысынан да, органикалық синтездің жаңа әдістерін жасау, сондай-ақ қосылыстардың жаңа қатарындағы молекулалардың стереохимиясын анықтау тұрғысынан да қызығушылық тудырады.

**Түйінді сөздер:** алкалоидтар, алкалоидтар туындылары, гибридті молекулалар, химиялық түрлендіру, цитизин, анабазин, эфедрин.

**Резюме**

## ГИБРИДНЫЕ МОЛЕКУЛЫ НА ОСНОВЕ АЛКАЛОИДОВ

***О.А. Нуркенов[1], С.Д. Фазылов[1,2], Г.К. Мукушева*[2], Е.В. Минаева[2], И.В. Кулаков[3], Ж.С. Нурмаганбетов[1], А.С. Кишкентаева[1], А.Р. Жасымбекова [2]***

*[1]«Институт органического синтеза и химии угля», Караганда, Казахстан*
*[2]НАО «Карагандинский университет имени Е.А. Букетова», Караганда, Казахстан*
*[3]ФГАОУ ВО «Тюменский государственный университет», Россия*
*E-mail: mukusheva1977@list.ru*

В представленном обзоре обобщены данные синтеза новых гибридных производных на основе молекул алкалоидов. При этом проанализированы методы получения гибридных структур, содержащих фрагменты молекул природных соединений в сочетании с другими биологически активными растительными метаболитами, в качестве соединений-лидеров для разработки новых фармакологически ценных агентов, с целью создания новых оригинальных лекарственных препаратов. Сочетание в одной молекуле фармакофорных остатков, а именно различных ароматических и гетероциклических заместителей в нуклеозидномположении природных алкалоидов раскрывает новые возможности как последующей химической модификации полученных полифункциональных производных, так и новую разнообразную их биологическую активность. На основе направленных превращений этих соединений (или их предшественников) разработаны эффективные методы синтеза. Перспективным является широкий спектр фармакологических свойств комбинированных соединений данных рядов при сочетании низкой токсичности. Учитывая, что получение комбинированных производных на основе молекул алкалоидов изучено недостаточно, направленный синтез новых соединений представляет интерес как в плане получения новых лекарственных веществ, так и разработки новых методов органического синтеза, а также определения стереохимии молекул нового ряда соединений.

**Ключевые слова:** алкалоиды, производные алкалоидов, гибридные молекулы, химическая модификация, цитизин, анабазин, эфедрин.

## *Ғылыми жарияланымдардың этикасы*

**Редакциялық алқа және "Қазақстанның химия журналы" ғылыми журналының (бұдан әрі – Журнал) бас редакторы "Жарияланымдар жөніндегі этика комитеті" (**Committee on Publication Ethics – COPE) (http://publicationethics.org/about), **"Еуропалық ғылыми редакторлар қауымдастығы"** (European Association of Science Editors – EASE) (http://www.ease.org.uk) **және "Ғылыми жарияланымдар әдебі жөніндегі комитеттің"** (http://publicet.org/code/) **қабылданған халықаралық стандарттарды ұстанады.**

Баспа қызметіндегі әділетсіз тәжірибені болдырмау мақсатында (плагиат, жалған ақпаратты ұсыну және т.б.) және ғылыми жарияланымдардың жоғары сапасын қамтамасыз ету, автордың алған ғылыми нәтижелерін жұртшылықпен тану мақсатында редакциялық кеңестің әрбір мүшесі, автор, рецензент, сондай-ақ баспа процесіне қатысатын мекемелер этикалық стандарттарды, нормалар мен ережелерді сақтауға және олардың бұзылуын болдырмау үшін барлық шараларды қабылдауға міндетті. Осы процеске қатысушылардың барлығының ғылыми жарияланым этикасы ережелерін сақтауы авторлардың зияткерлік меншік құқықтарын қамтамасыз етуге, басылым сапасын арттыруға және авторлық материалдарды жеке тұлғалардың мүддесі үшін заңсыз пайдалану мүмкіндігін болдырмауға ықпал етеді.

Редакцияға келіп түскен барлық ғылыми мақалалар міндетті түрде екі жақты шолудан өтеді. Журнал редакциясы мақаланың журнал профиліне, ресімдеу талаптарына сәйкестігін белгілейді және оны қолжазбаның ғылыми құндылығын айқындайтын және мақала тақырыбына неғұрлым жақын ғылыми мамандандырулары бар екі тәуелсіз рецензент – мамандарды тағайындайтын журналдың жауапты хатшысының бірінші қарауына жібереді. Мақалаларды рецензиялауды редакциялық кеңес және редакциялық алқа мүшелері, сондай-ақ басқа елдердің шақырылған рецензенттері жүзеге асырады. Мақалаға сараптама жүргізу үшін белгілі бір рецензентті таңдау туралы шешімді Бас редактор қабылдайды. Рецензиялау мерзімі 2-4 аптаны құрайды, бірақ рецензенттің өтініші бойынша ол ұзартылуы мүмкін.

**Редакция мен рецензент** қарауға жіберілген жарияланбаған материалдардың құпиялылығын сақтауға кепілдік береді. Жариялау туралы шешімді журналдың редакциялық алқасы рецензиялаудан кейін қабылдайды. Қажет болған жағдайда қолжазба авторларға рецензенттер мен редакторлардың ескертулері бойынша пысықтауға жіберіледі, содан кейін ол қайта рецензияланады. Редакция этика ережелерін бұзған жағдайда мақаланы жариялаудан бас тартуға құқылы. Егер ақпаратты плагиат деп санауға жеткілікті негіз болса, жауапты редактор жариялауға жол бермеуі керек.

**Авторлар** редакцияға ұсынылған материалдардың жаңа, бұрын жарияланбаған және түпнұсқа екендігіне кепілдік береді. Авторлар ғылыми нәтижелердің сенімділігі мен маңыздылығына, сондай-ақ ғылыми этика қағидаттарын сақтауға, атап айтқанда, ғылыми этиканы бұзу фактілеріне жол бермеуге (ғылыми деректерді тұжырымдау, зерттеу деректерін бұрмалауға әкелетін бұрмалау, плагиат және жалған тең авторлық, қайталау, басқа адамдардың нәтижелерін иемдену және т. б.) жауапты болады.

Мақаланы редакцияға жіберу авторлардың мақаланы (түпнұсқада немесе басқа тілдерге немесе басқа тілдерге аударылған) басқа журналға(журналдарға) берме-

генін және бұл материал бұрын жарияланбағанын білдіреді. Әйтпесе, мақала авторларға авторлық құқықты бұзғаны үшін мақаланы қабылдамау туралы ұсыныспен дереу қайтарылады. Басқа автор жұмысының 10 пайызынан астамын оның авторлығын және дереккөзге сілтемесіз сөзбе-сөз көшіруге жол берілмейді. Алынған фрагменттер немесе мәлімдемелер автор мен бастапқы көзді міндетті түрде көрсете отырып жасалуы керек. Шамадан тыс көшіру, сондай-ақ кез-келген нысандағы плагиат, оның ішінде рәсімделмеген дәйексөздер, өзгерту немесе басқа адамдардың зерттеулерінің нәтижелеріне құқықтар иемдену этикалық емес және қолайсыз. Зерттеу барысына қандай да бір түрде әсер еткен барлық адамдардың үлесін мойындау қажет, атап айтқанда, мақалада зерттеу жүргізу кезінде маңызды болған жұмыстарға сілтемелер ұсынылуы керек. Қосалқы авторлардың арасында зерттеуге қатыспаған адамдарды көрсету болмайды.

Егер жұмыста қате табылса, редакторға тез арада хабарлау керек және бірге түзету туралы шешім қабылдау керек.

Қолжазбаны жариялаудан бас тарту туралы шешім рецензенттердің ұсынымдарына сәйкес редакциялық алқа отырысында қабылданады. Редакциялық алқаның шешімімен жариялауға ұсынылмаған мақала қайта қарауға қабылданбайды. Жариялаудан бас тарту туралы хабарлама авторға электрондық пошта арқылы жіберіледі.

Редакциялық алқа мақаланы жариялауға жіберу туралы шешім қабылдағаннан кейін редакция бұл туралы авторға хабарлайды және жариялау мерзімін көрсетеді. Рецензиялардың түпнұсқалары журналдың редакциясында 3 жыл бойы сақталады.

## *Этика научных публикаций*

**Редакционная коллегия и главный редактор научного журнала «Химическийжурнал Казахстана» (далее – Журнал) придерживаются принятых международных стандартов «Комитета этики по публикациям» (**Committee on Publication Ethics – COPE) (http://publicationethics.org/about), **«Европейской ассоциации научных редакторов»** (European Association of Science Editors – EASE) (http://www.ease.org.uk) и «**Комитета по этике научных публикаций**» (http://publicet.org/code/).

Во избежание недобросовестной практики в публикационной деятельности (плагиат, изложение недостоверных сведений и др.) и в целях обеспечения высокого качества научных публикаций, признания общественностью, полученных автором научных результатов, каждый член редакционного совета, автор, рецензент, а также учреждения, участвующие в издательском процессе, обязаны соблюдать этические стандарты, нормы и правила и принимать все меры для предотвращения их нарушений. Соблюдение правил этики научных публикаций всеми участниками этого процесса способствует обеспечению прав авторов на интеллектуальную собственность, повышению качества издания и исключению возможности неправомерного использования авторских материалов в интересах отдельных лиц.

Все научные статьи, поступившие в редакцию, подлежат обязательному двойному слепому рецензированию. Редакция Журнала устанавливает соответствие статьи профилю Журнала, требованиям к оформлению и направляет ее на первое рассмотрение ответственному секретарю Журнала, который определяет научную ценность рукописи и назначает двух независимых рецензентов – специалистов, имеющих наиболее близкие к теме статьи научные специализации. Рецензирование статей осуществляется членами редакционного совета и редакционной коллегии, а также приглашенными рецензентами других стран. Решение о выборе того или иного рецензента для проведения экспертизы статьи принимает главный редактор. Срок рецензирования составляет 2-4 недели, но по просьбе рецензента он может быть продлен.

**Редакция и рецензент** гарантируют сохранение конфиденциальности неопубликованных материалов присланных на рассмотрение работ. Решение о публикации принимается редакционной коллегией Журнала после рецензирования. В случае необходимости рукопись направляется авторам на доработку по замечаниям рецензентов и редакторов, после чего она повторно рецензируется. Редакция оставляет за собой право отклонить публикацию статьи в случае нарушения правил этики. Ответственный редактор не должен допускать к публикации информацию, если имеется достаточно оснований полагать, что она является плагиатом.

**Авторы** гарантируют, что представленные в редакцию материалы являются новыми, ранее неопубликованными и оригинальными. Авторы несут ответственность за достоверность и значимость научных результатов, а также соблюдение принципов научной этики, в частности, недопущение фактов нарушения научной этики (фабрикация научных данных, фальсификация, ведущая к искажению исследовательских данных, плагиат и ложное соавторство, дублирование, присвоение чужих результатов и др.)

Направление статьи в редакцию означает, что авторы не передавали статью (в оригинале или в переводе на другие языки или с других языков) в другой журнал(ы)

и что этот материал не был ранее опубликован. В противном случае статья немедленно возвращается авторам с рекомендацией отклонить статью за нарушение авторских прав. Не допускается дословное копирование более 10 процентов работы другого автора без указания его авторства и ссылок на источник. Заимствованные фрагменты или утверждения должны быть оформлены с обязательным указанием автора и первоисточника. Чрезмерные заимствования, а также плагиат в любых формах, включая неоформленные цитаты, перефразирование или присвоение прав на результаты чужих исследований, неэтичны и неприемлемы. Необходимо признавать вклад всех лиц, так или иначе повлиявших на ход исследования, в частности, в статье должны быть представлены ссылки на работы, которые имели значение при проведении исследования. Среди соавторов недопустимо указывать лиц, не участвовавших в исследовании.

Если обнаружена ошибка в работе, необходимо срочно уведомить редактора и вместе принять решение об исправлении.

Решение об отказе в публикации рукописи принимается на заседании редакционной коллегии в соответствии с рекомендациями рецензентов. Статья, не рекомендованная решением редакционной коллегии к публикации, к повторному рассмотрению не принимается. Сообщение об отказе в публикации направляется автору по электронной почте.

После принятия редколлегией Журнала решения о допуске статьи к публикации редакция информирует об этом автора и указывает сроки публикации. Оригиналы рецензий хранятся в редакции Журнала в течение 3 лет.

## *Ethics of scientific publications*

**The editorial board and editor-in-chief of the scientific journal "Chemical Journal of Kazakhstan" (hereinafter - the Journal) adhere to the accepted international standards of "the Committee on Publication Ethics" (COPE)** (http://publicationethics.org/about), **"European Association of Science Editors – EASE"** (http://www.ease.org.uk) **and"Committee on the Ethics of Scientific Publications"** (http://publicet.org/code/).

Public recognition of the scientific results obtained by the author, each member of the editorial board, author, reviewer, as well as institutions involved in the publishing process is obliged to comply with ethical standards, norms, and rules and take all measures to prevent violations thereof. This is needed to avoid unfair practice in publishing activities (plagiarism, presentation of false information, etc.) and to ensure the high quality of scientific publications. Compliance with the rules of ethics of scientific publications by all participants in this process contributes to ensuring the rights of authors to intellectual property, improving the quality of the publication, and excluding the possibility of illegal use of copyright materials in the interests of individuals.

All scientific articles submitted to the editorial office are subject to mandatory double-blind review. The editorial board of the Journal establishes the correspondence of the article to the profile of the Journal, the requirements for registration and sends it for the first consideration to the executive secretary of the Journal, who determines the scientific value of the manuscript and appoints two independent reviewers - specialists who have scientific specializations closest to the topic of the article. Reviewing of articles is carried out by members of the editorial board and editorial board, as well as invited reviewers from other countries. The decision on choosing a reviewer for the examination of the article is made by the editor-in-chief. The review period is 2-4 weeks, but it can be extended at the request of the reviewer.

**The editorial board and the reviewer** guarantee the confidentiality of unpublished materials sent for consideration. The decision on publication is made by the editorial board of the Journal after reviewing. The manuscript is sent to the authors for revision based on the comments of reviewers and editors if necessary. After which, it is re-reviewed. The editors reserve the right to reject the publication of an article in case of a violation of the rules of ethics. The executive editor should not allow information to be published if there are sufficient grounds to believe that it is plagiarism.

**The authors** guarantee that the submitted materials to the editorial office are new, previously unpublished, and original. Authors are responsible for the reliability and significance of scientific results, as well as adherence to the principles of scientific ethics, in particular, the prevention of violations of scientific ethics (fabrication of scientific data, falsification leading to distortion of research data, plagiarism, and false co-authorship, duplication, appropriation of other people's results, etc.).

The submission of an article to the Editorial Board means that the authors did not transmit the article (in original or translation into other languages or from other languages) to another journal (s), and this material has not been previously published. Otherwise, the article is immediately returned to the authors with a recommendation to reject the article for copyright infringement. Verbatim copying of more than 10 percent of another author's work is not allowed without indicating his authorship and links to the source. Borrowed fragments or statements must be made with the obligatory indication of

the author and the source. Excessive borrowing as well as plagiarism in any form, including unofficial quotations, paraphrasing, or appropriation of rights to the results of other people's research, is unethical and unacceptable. It is necessary to recognize the contribution of all persons, who in one way or another influenced the course of the research in particular the article, should contain references to works that were of importance in the conduct of the research. Among the co-authors, it is inadmissible to indicate persons who did not participate in the study.

If an error is found in work, it is necessary to notify the editor and together make a decision on the correction.

The decision to refuse publication of the manuscript is made at a meeting of the editorial board by the recommendations of the reviewers. An article not recommended for publication by the decision of the editorial board is not accepted for reconsideration. The refusal to publish is sent to the author by e-mail.

After the editorial board of the Journal decides on the admission of the article for publication, the editorial board informs the author about it and indicates the terms of publication. The originals of the reviews are kept in the editorial office for three years.

Технический секретарь *К. Д. Мустафинов*

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