ISSN 2518-1491 (Online),
ISSN 2224-5286 (Print)

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ

Д.В.СОКОЛЬСКИЙ АТЫНДАҒЫ «ЖАНАРМАЙ,
КАТАЛИЗ ЖӘНЕ ЭЛЕКТРОХИМИЯ ИНСТИТУТЫ» АҚ

Х А Б А Р Л А Р Ы

ИЗВЕСТИЯ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН

АО «ИНСТИТУТ ТОПЛИВА, КАТАЛИЗА И
ЭЛЕКТРОХИМИИ ИМ. Д.В. СОКОЛЬСКОГО»

N E W S

OF THE ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN

JSC «D.V. SOKOLSKY INSTITUTE OF FUEL,
CATALYSIS AND ELECTROCHEMISTRY»

ХИМИЯ ЖӘНЕ ТЕХНОЛОГИЯ СЕРИЯСЫ

♦

СЕРИЯ ХИМИИ И ТЕХНОЛОГИИ

♦

SERIES CHEMISTRY AND TECHNOLOGY

4 (430)

ШІЛДЕ – ТАМЫЗ 2018 ж.
ИЮЛЬ – АВГУСТ 2018 г.
JULY-AUGUST 2018

1947 ЖЫЛДЫҢ ҚАҢТАР АЙЫНАН ШЫҒА БАСТАҒАН
ИЗДАЕТСЯ С ЯНВАРЯ 1947 ГОДА
PUBLISHED SINCE JANUARY 1947

ЖЫЛЫНА 6 РЕТ ШЫҒАДЫ
ВЫХОДИТ 6 РАЗ В ГОД
PUBLISHED 6 TIMES A YEAR

АЛМАТЫ, ҚР ҰҒА АЛМАТЫ, НАН РК ALMATY, NAS RK

NAS RK is pleased to announce that News of NAS RK. Series of chemistry and technologies scientific journal has been accepted for indexing in the Emerging Sources Citation Index, a new edition of Web of Science. Content in this index is under consideration by Clarivate Analytics to be accepted in the Science Citation Index Expanded, the Social Sciences Citation Index, and the Arts & Humanities Citation Index. The quality and depth of content Web of Science offers to researchers, authors, publishers, and institutions sets it apart from other research databases. The inclusion of News of NAS RK. Series of chemistry and technologies in the Emerging Sources Citation Index demonstrates our dedication to providing the most relevant and influential content of chemical sciences to our community.

Қазақстан Республикасы Ұлттық ғылым академиясы "ҚР ҰҒА Хабарлары. Химия және технология сериясы" ғылыми журналының Web of Science-тің жаңаланған нұсқасы Emerging Sources Citation Index-те индекстелуге қабылданғанын хабарлайды. Бұл индекстелу барысында Clarivate Analytics компаниясы журналды одан әрі the Science Citation Index Expanded, the Social Sciences Citation Index және the Arts & Humanities Citation Index-ке қабылдау мәселесін қарастыруда. Webof Science зерттеушілер, авторлар, баспашылар мен мекемелерге контент тереңдігі мен сапасын ұсынады. ҚР ҰҒА Хабарлары. Химия және технология сериясы Emerging Sources Citation Index-ке енуі біздің қоғамдастық үшін ең өзекті және беделді химиялық ғылымдар бойынша контентке адалдығымызды білдіреді.

НАН РК сообщает, что научный журнал «Известия НАН РК. Серия химии и технологий» был принят для индексирования в Emerging Sources Citation Index, обновленной версии Web of Science. Содержание в этом индексировании находится в стадии рассмотрения компанией Clarivate Analytics для дальнейшего принятия журнала в the Science Citation Index Expanded, the Social Sciences Citation Index и the Arts & Humanities Citation Index. Web of Science предлагает качество и глубину контента для исследователей, авторов, издателей и учреждений. Включение Известия НАН РК в Emerging Sources Citation Index демонстрирует нашу приверженность к наиболее актуальному и влиятельному контенту по химическим наукам для нашего сообщества.

«ҚР ҰҒА Хабарлары. Химия және технология сериясы».
ISSN 2518-1491 (Online),
ISSN 2224-5286 (Print)
Меншіктенуші: «Қазақстан Республикасының Ұлттық ғылым академиясы» Республикалық қоғамдық бірлестігі (Алматы қ.)
Қазақстан республикасының Мәдениет пен ақпарат министрлігінің Ақпарат және мұрағат комитетінде 30.04.2010 ж. берілген **№1089-Ж** мерзімдік басылым тіркеуіне қойылу туралы куәлік

Мерзімділігі: жылына 6 рет.
Тиражы: 300 дана.

Редакцияның мекенжайы: 050010, Алматы қ., Шевченко көш., 28, 219 бөл., 220, тел.: 272-13-19, 272-13-18,
www:nauka-nanrk.kz / chemistry-technology.kz

Типографияның мекенжайы: «Аруна» ЖК, Алматы қ., Муратбаева көш., 75.

«Известия НАН РК. Серия химии и технологии».
ISSN 2518-1491 (Online),
ISSN 2224-5286 (Print)
Собственник: Республиканское общественное объединение «Национальная академия наук Республики Казахстан» (г. Алматы)
Свидетельство о постановке на учет периодического печатного издания в Комитете информации и архивов Министерства культуры и информации Республики Казахстан **№10893-Ж,** выданное 30.04.2010 г.

Периодичность: 6 раз в год
Тираж: 300 экземпляров

Адрес редакции: 050010, г. Алматы, ул. Шевченко, 28, ком. 219, 220, тел. 272-13-19, 272-13-18,
http://nauka-nanrk.kz / chemistry-technology.kz

Адрес редакции: 050100, г. Алматы, ул. Кунаева, 142,
Институт органического катализа и электрохимии им. Д. В. Сокольского,
каб. 310, тел. 291-62-80, факс 291-57-22, e-mail:orgcat@nursat.kz
Адрес типографии: ИП «Аруна», г. Алматы, ул. Муратбаева, 75

News of the National Academy of Sciences of the Republic of Kazakhstan. Series of chemistry and technology.
ISSN 2518-1491 (Online),
ISSN 2224-5286 (Print)
Owner: RPA "National Academy of Sciences of the Republic of Kazakhstan" (Almaty)
The certificate of registration of a periodic printed publication in the Committee of Information and Archives of the Ministry of Culture and Information of the Republic of Kazakhstan N 10893-Ж, issued 30.04.2010

Periodicity: 6 times a year
Circulation: 300 copies

Editorial address: 28, Shevchenko str., of. 219, 220, Almaty, 050010, tel. 272-13-19, 272-13-18,
http://nauka-nanrk.kz / chemistry-technology.kz

Editorial address: Institute of Organic Catalysis and Electrochemistry named after D. V. Sokolsky
142, Kunayev str., of. 310, Almaty, 050100, tel. 291-62-80, fax 291-57-22,
e-mail: orgcat@nursat.kz

Address of printing house: ST "Aruna", 75, Muratbayev str, Almaty

N E W S
OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN
SERIES CHEMISTRY AND TECHNOLOGY
ISSN 2224-5286
Volume 4, Number 430 (2018), 85 – 98

UDC 577.127:547.973

O.A. Nurkenov[1,2], M.K. Ibrayev[2], S.D. Fazylov[1], A.T. Takibayeva[2], I.V. Kulakov[3], A.E. Tuktybayeva[2]

[1]Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, Karaganda, Kazakhstan;
[2]Karaganda State Technical University, Karaganda, Kazakhstan;
[3] Dostoevsky Omsk State University, Omsk,Russia
E-mail: nurkenov_oral@mail.ru, altynarai81@mail.ru

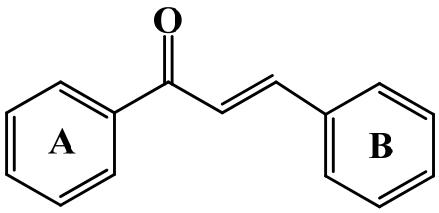
CHALCONES-SYNTHONS IN SYNTHESIZING BIOLOGICALLY ACTIVE MATTERS

Abstract. The review paper summarizes and systematizes the literature data of recent years, as well as the results of the authors' research in the field of functionally substituted chalcones. The most common natural chalcones, methods of production, reactivity and biological properties of synthetic chalcones are given.

Keywords: substituted aromatic aldehyde, chalcone, pyrazoline, flavonone, cytokine, NF-κB transcription factor.

Important representatives of organic compounds having a preparative value are α, β-unsaturated carbonyl compounds, among which benzylideneacetophenones (chalcones) occupy a notable place. Since the discovery in 1896 of chalcones [1], the interest in the chemistry of its substituted and heterocyclic analogs has not faded. The name "chalkone" was proposed by the Polish chemist Stanislav Kostanecki. It comes from the Greek word *"chalcos"(χαλκός)* that means "copper".

Chalcones 1,3-diphenyl-2-propen-1-ons (1) belong to the compounds in which two aromatic nuclei are bound by three carbon atoms of the α, β-unsaturated carbonyl system [2]. Chalcones can have *cis*- and *trans*-forms, but the *trans*-form is thermodynamically more stable.



1

1. Widespread natural chalcones

Chalcones are quite widespread in nature: they are found in flowers, fruits, seeds, and wood. They are closely related to a number of substances that belong to the class of flavonoids: flavones, flavonones, flavonols. Most of the representatives of the chalcones are found in all plant organs in the form of aglycones and glycosides and differ in the number of substituents in the A ring. So, for example, butein chalcone that is often found in the family of comatose chalcones, is in the form of *Coreopsis giganiea* 4-glycoside; chalconoraine is in the form of 2-glycoside isosalipurposide in *Salix purpyrea* [3, 4]. By now more than 200 different aglicones of the chalconic nature are known. Quite often dihydrochalcones are found in plants, in which the three-carbon fragment has a reduced double bond. They are known exclusively in glycosidized form, as well as methoxy- and pyrano-derivatives. So, some species of apple

tree contain glycoside phloridzin (2'-glucoside, 4', 2', 4,6-tetraoxidyhydrochalcone) that causes intensive release of glucose from the body in a person (phluoridinine diabetes), siboldin (3-hydroxyfloretin-4'-glucoside), azepogenin in the form of azobothin 2'-glycoside [4]. It is believed that chalcones are precursors of various groups of flavonoid compounds in biosynthesis.

Many bright colors of the plant world of our planet in spring, summer and autumn are caused by compounds of one flavonoid class, i.e. chalcones. They are called "antichloropigments", they are yellow pigments of flowers that turn orange in pairs of ammonia. In particular, discoloration of the contained chalcones of the preparative forms is used in the field of pharmaceuticals, for example as a color-changing oral care component that can be phenyl-3-methoxy-4-hydroxystyryl ketone and 3-(4'-hydroxy-3'-methoxy)1-phenylprop-2-en-1-on [5]. Chalcones are relatively often found in one family: *Compositae*, especially in *Coreopsis* and *Dahlia.* They are also found in some *Leguminosae (Butia, Cylicodiscus, Glycyrhiza, Plathymenia, Ulex)* and in *Dihymocarpus (Gesneriaceae).* Table 1 lists some chalcones and their derivatives isolated from natural raw materials.

Table 1- Chalconesandtheirderivativesisolatedfromnaturalsources

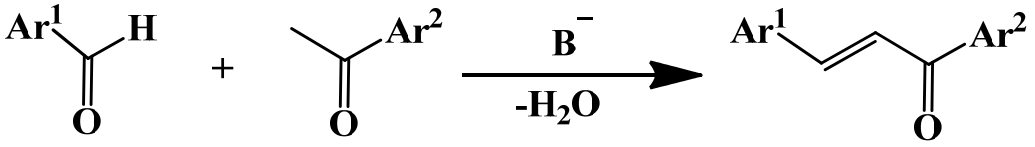
No	Chalcones and their derivatives	Natural sources	Reference
1	2'-hydroxy-2,4,6-trimethoxychalcone	*Andrographis lincate (Acanthaceae)*	[6]
2	2', 4'-dihydroxy-4-methoxydihydroalchalcone (davidigenin)	*Artemisia dracuiiculus L. (Asteraceae)*	[7]
3	2 ', 4', 4-trihydroxy-3 '- [6-hydroxy-3,7-dimethyl-2 (E) -7-octadienyl] chalcone	*Artocarpus nobilis*	[8; 9]
4	2 ', 4', 6 ', 4-tetrahydroxychalcone (isosalipurpol);	*Arabidopsis thaliana (Angiosperm)*	[10; 11; 12; 13]
5	2 & apos;, 4 & apos;, 4-trihydroxychalcone (iso-liquitytigenin)	*Asarum canadense (Aristolochiaceae)*	[14]
6	chalcononanerenine 2'-O-β-D-glucoside-4'-O-β-gentobiose; 2 ', 4'-di-O-β-D-glucoside	*Boesenbergia pandurata (Robx.)*	[15]
7	2', 6'-dihydroxy-4'-methoxychalcone;	*Brassica alba (Cruciferae)*	[16]
8	2'-hydroxy-4,4'6'-trimethoxychalcone	*Caesalpinia pulcherrima L.*	[17]
9	4-hydroxy-2 ', 4'-dimethoxy dihydroqualone; isocyclitis	*Crinum bulbispermum bulbs.*	[18]
10	4,4'-bis-a-0-glucosyl-4,2 ', 4'-trihydroxy-6, -methoxychalcon (aglycone)	*Derodendron phlomidis (Vcrbenaceae)*	[19]
11	3'- (3 "-methyl-3" -hydroxybutyl) -2', 4,4'-trihydroxy-6'-methoxychalcone; 4'-O-glucuronyl-2,4-dihydroxy-6'-methoxy-3'-prenylalkalkone; 1 - [(2 ', 4'-dihydroxy-3'-isoprenyl-6'-methoxy) -phenyl] - [3- (4-hydroxyphenyl)] - 2,3-epoxypropan-1-one; 4-acetoxy-2 ', 4'-dihydroxin-6'-methoxy-3'-prenylalkalcon; 1 - [(2', 4'-dihydroxy-3'-isoprenyl-6'-methoxy) -phenyl] - [3- (4-hydroxyphenyl)] - 2,3-epoxypropan-1-one; 4-acetoxy-2', 4'-dihydroxin-6'-methoxy-3'-prenylalchalcone	*Humulus lupulus L. (Cannabaceae)*	[20; 21]
12	4', 6', 4-trihydroxy-5-methoxychalcone; 4 ', 6'-dihydroxy-4, 5-dimethoxychalcone	*Iryanthcra polyneura (Myristicaceae)*	[22]
13	2', 4', 6'-trihydroxy-4-methoxydihydrochalcone;	*Iryanthcra virola (Myristicaceae)*	[22]
14	2'-megoxy-4 ', 6', 4-trihydroxidehydrochalcone;	*Iryanthera sagotiana (Myristicaceae)*	[22]
15	2', 4-dimethoxy-4', b'-dihydroxydihydrochalcone;	*Marchantia paleaceae*	[10]
16	2'-glucoside-4 ', 6'-dihydroxy-4-methoxy-dihydro-chalcone; 4 ', 6', 4-trihydroxy-5-methoxydihydro-chalcone; 2', 4, 5-trimethoxy-4', 6'-dihydroxydi-hydrohalcon; 4 ', 4-dimethoxy-6'-α-dihydroxydi-hydrochalcone	*Medicago sativa L.*	[10; 12]
17	Bi-2 ', 4', 6'-trihydroxy-4-methoxydehydrochalcone	*Mellettia ferruginea (Fabaceae)*	[23]
18	2', 4', 6', 4-tetrahydroxychalcone (naringenin)	*Vitis vinifera (Angiosperm)*	[12; 24]

2. Methods of obtaining synthetic chalcones

Synthetic chalcones are of considerable interest for chemists and pharmacists, which is due to several factors: the comparative simplicity of the chemical structure that allows synthesizing on their base a large

variety of molecules with high pharmacological activity, as well as the possibility of using them as valuable synthetic intermediates, for example, in the synthesis of various heterocyclic compounds. It should be noted that α, β-unsaturated ketone groups are probably responsible for most of the observed biological properties of chalcones, since these groups are present in all biologically active molecules, and their removal is associated with losing activity [25]. Many authors attribute the presence of this fragment to the different biological activity of the substituted chalcones: anti-inflammatory [26], antitubercular [27], antioxidant, antiviral, antimicrobial, antifungal and many other activities [28, 29]. Substituted chalcones are promising antitumor preparations [30, 31]. They also attract attention as preparations that have selective activity against dermatophytes [32]. Substituted chalcones are of interest as components for solar cells [33], ion-selective electrodes, molecular devices and photofunctional materials [34-38].

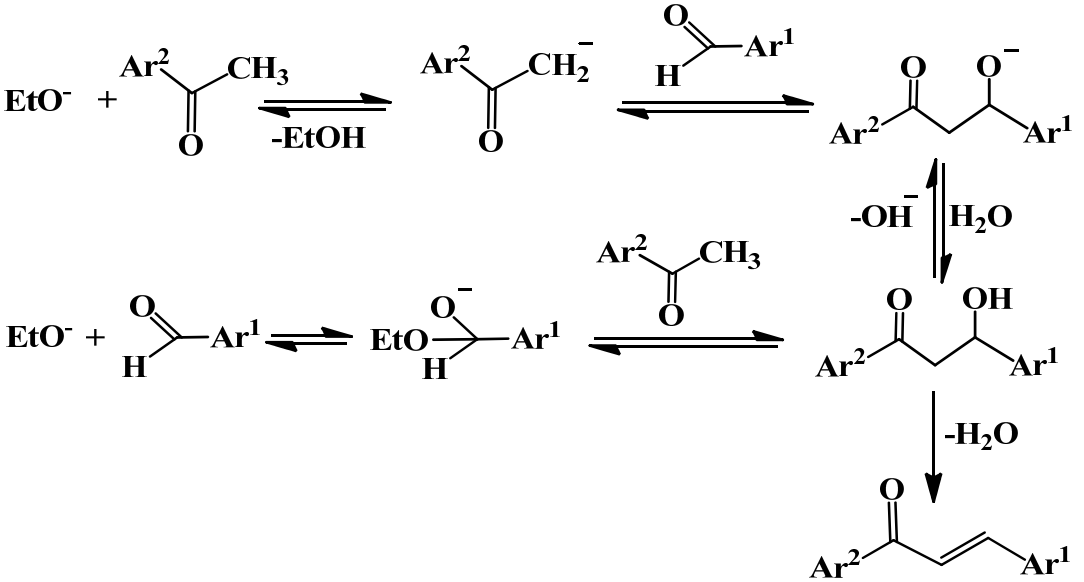
The most significant method of synthesizing chalcones is known [39] the croton condensation involving formyl- and acetyl-containing compounds. According to the Claisen-Schmidt reaction, from 32 substituted acetophenones and 40 aromatic benzaldehydes there were obtained 1280 substituted chalcones by combinatorial synthesis methods. The use of these chalcones in 9 condensation and cyclization reactions led to producing 74,000 five- and six-membered cyclic compounds [40].



Ar^1, Ar^2 = Ph, substituted phenyls, heterocycles

When studying the Claisen-Schmidt reaction using the UV spectroscopy method, it was found that the interaction of substituted benzaldehydes with acetophenone is described by the second-order velocity equation. In this connection the authors of [41] proposed two reaction mechanisms. The first one is through removing acetophenone by the proton base from the methyl group (mechanism I), the second one is through attacking the ethylate anion on the carbon of the carbonyl group of the aldehyde (mechanism II). Using the thermodynamic parameters in the discussion of each stage of the proposed mechanisms, the authors concluded that the mechanism II should be more profitable [41]:

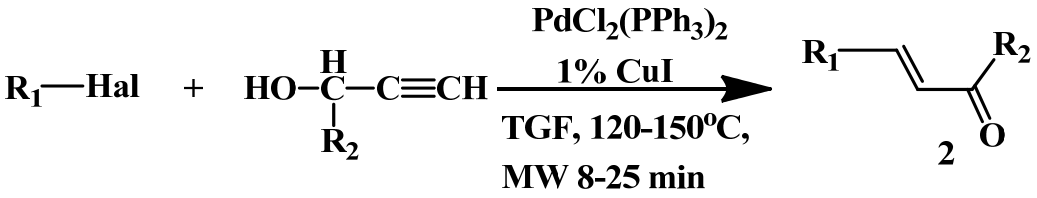
MechanismI

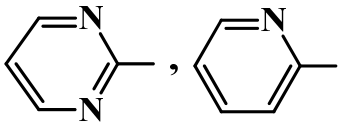


Ar^1, Ar^2 = Ph, substituted phenyls, heterocycles

But in some cases, with the use of substituted chalcones, this method is accompanied by side oxidation-reduction processes leading to reducing the yield of the desired product. In literature a large number of methods for synthesizing chalcones using homogeneous and heterogeneous catalysis techniques have been described [42, 43], among which the catalysis with activated barium hydroxide [44], hydrochloric acid formed in situ by interaction of $SOCl_2$ in absolute EtOH [45], BF_3-Et_2O [46], potassium hydroxide deposited on KF-Al_2O_3 in combination with ultrasonic irradiation, ionic liquids [47, 48]. There are known works using microwave irradiation, using metal oxides, I_2-Al_2O_3 without using solvents, which reduced the reaction time from 3 hours to 80 seconds [49, 50]. These conditions allow getting rid of unwanted reaction products [51], increasing the yield and shortening the reaction time to several minutes.

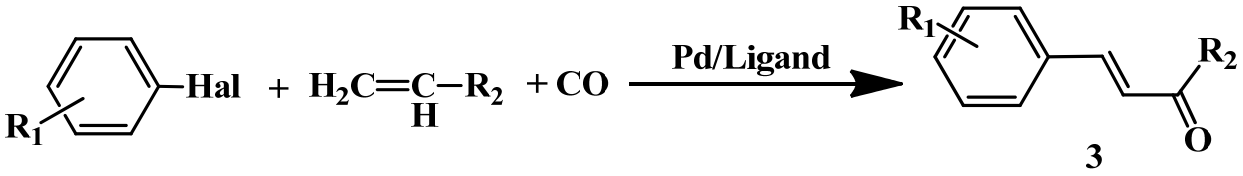
In addition to the Claisen-Schmidt reaction, alternative waysof synthesizing substituted chalcones are described in literature, which make it possible to obtain them with high yields under mild conditions. In some cases the methods allow avoiding undesirable redox processes or obtaining compounds not available in the classical Claisen-Schmidt reaction. However, in this case, as a rule, expensive reagents are required, the use of microwave or ultrasound exposure and inert atmosphere. Thus, for synthesizing chalcones 2, there was used the Sonogashira coupling reaction under microwave conditions between the aryl halide and substituted propargyl alcohol, which allowed producing the target products with high yields in a short time [26]. It was shown that the reaction proceeded only in the presence of an electron-withdrawing group as a substituent in the aromatic nucleus R_1.



R_1 = Ph, 4-CN-Ph, 4-EtO_2C-Ph, 3-NH_2Ph, 

R_2 = Ph, 2-tienyl, 3-tienyl, C_3H_8,

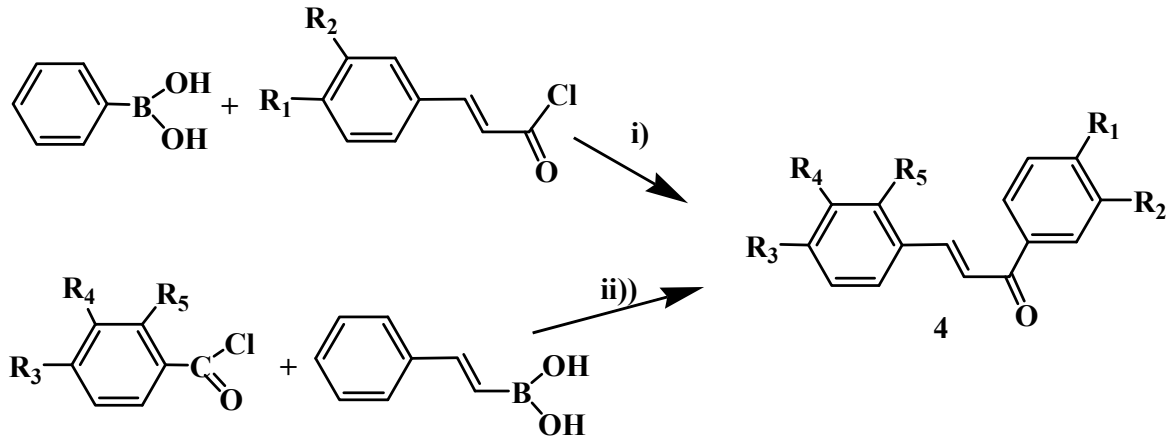
In [52] there are presented the data of the Heck coupling-carbonylation reaction involving aryl halide and styrene or substituted vinyl in the presence of carbon monoxide using a palladium catalyst leading to formation of chalcones 3. It is shown that the yields of the product 3 make 41-90%, depending on using the ligand and a substituent in the aromatic ring of the chalcone.



R_1 = H, 4-CH_3, 2-t-Bu, 2-CH_3, 4-CF_3, 4-Br, 4-Cl, 4-CO_2Me, 4-OCH_3, 3,4-O-CH_2-CH_2-O, 4-OEt

R_2 = Ph, 4-t-BuPh, 3-CH_3Ph, 4-CH_3OPh, 4-ClPh, 4-FPh, -C(O)-O-nBu, -O-nBu

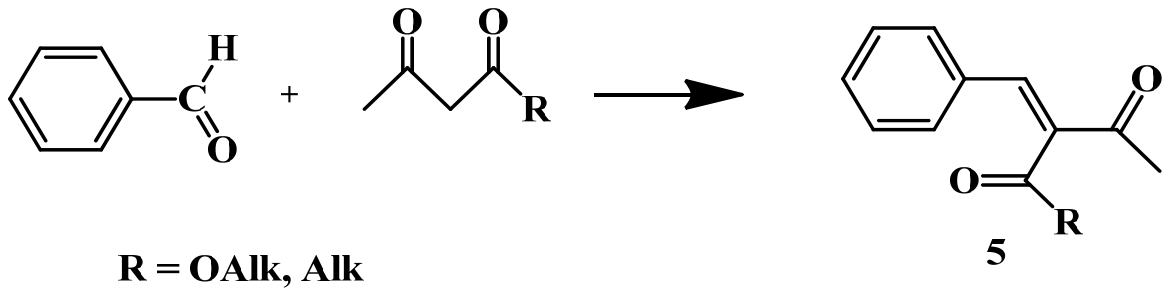
The authors of Ref. [53] obtained chalcones 4 under mild conditions using several variants of the Suzuki reaction: the first one using cinnamoyl chloride and phenylboronic acid, and the other with benzoyl chloride and phenyl vinyl boric acid. Both reactions led to the desired product 4.



R_1 = H, OCH_3; R_2 = H, NO_2, OCH_3;
R_3 = H, OCH_3; R_4 = H, CF_3, NO_2, OCH_3; R_5 = H, CF_3

i): $(PPh_3)_4Pd(o)$, Cs_2CO_3, toluol. Yield 40-50%
ii)): $(PPh_3)_4Pd(o)$, Cs_2CO_3, toluol.Yield 70-95%

Chalcones can also be obtained by the Knoevenagel condensing, i.e. interaction of aldehydes or ketones with compounds having an active methylene component, for example, acetoacetic ether under conditions of the basic catalysis [39]. This reaction with interaction of benzaldehyde with AAE leads to the formation of chalcone 5.



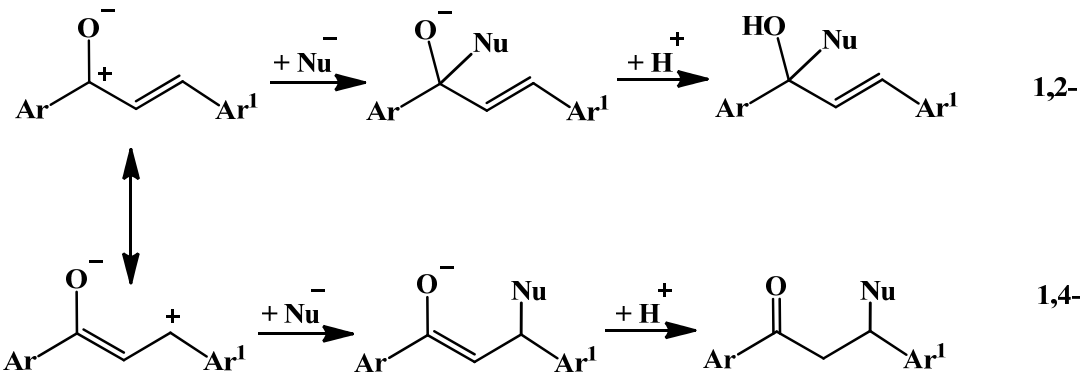
R = OAlk, Alk

Despite a large amount of literature dealing with optimization of methods for synthesizing chalcones, a lot of authors use an exclusively traditional method of synthesis, i.e. Claisen-Schmidt condensation (mixing under basic conditions in ethanol within 3-48 hours) [31, 34-37, 54].

3. Reactivity of chalcones

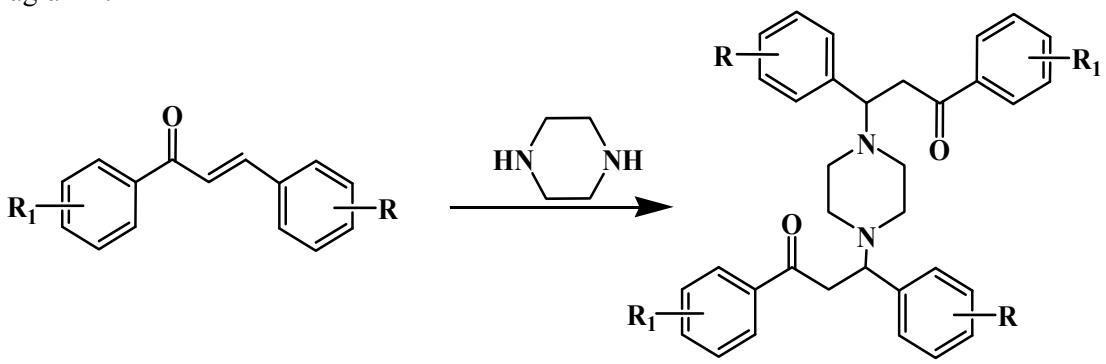
Chalcones possess high reactivity. This is connected with the presence in their molecule of two electrophilic centers:a carbonyl group and aβ-carbon atom of the conjugated double bond [1]. Chalcones can react as ambiguous electrophiles as a result of delocalization of the electron density in the conjugate system C = C-C = O. When interacting with the chalcone, the nucleophile attacks either the carbon atom of the carbonyl group (1,2-addition) or the β-carbon atom (1,4-addition); the mechanism of the reactions is shown in Diagram 1. The nature of these two electrophilic centers in chalcones is different, which is reflected in the high regioselectivity of reactions with mono- and binucleophiles.

Diagram 1



The interaction of chalcones with piperazine usually leads to the formation of Michael bis-aza-adducts. These reactions performed under various conditions, have been repeatedly described in literature as an example of forming a carbon-nitrogen bond [55-57]. Thus, chalcones, both unsubstituted and substituted, react with anhydrous piperazine in toluene giving the corresponding Michael bis-aza-adducts [55]. Similarly there takes place a reaction in the mixture of cyclohexane ether (1:2) in the presence of calcined potassium carbonate [56]. Under ultrasonic irradiation chalcones interact with piperazine in water, also forming Michael bis-aza-adduct with a high yield [57].

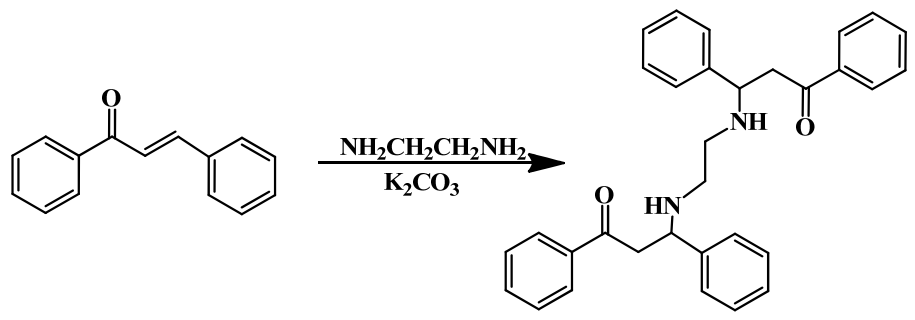
Diagram 2.



R_1=R=H; R_1=H, R=3-NO_2; R_1=H, R=2-Cl; R_1=4-Cl, R=H; R_1=H, R=4-Cl; R_1=R=4-Cl; R_1=4-Br, R=H; R_1=H, R=4-Me; R_1=4-Me, R=H; R_1=H, R=4-OMe; R_1=R=4-Me; R_1=4-Me, R=4-OMe; $C_6H_5CH_3$.

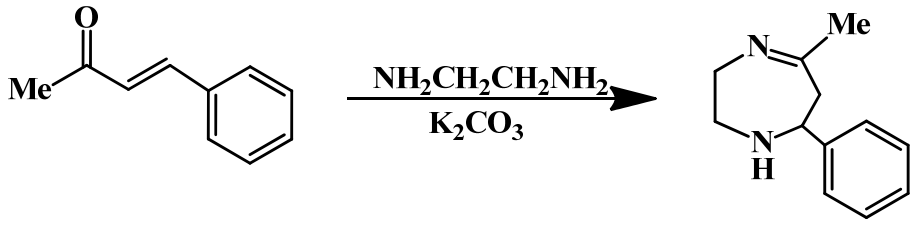
The reactions of chalcones with ethylenediamine can proceed with forming Michael bis-aza-adducts [56] or diazepines [58, 59]. Thus, the interaction of unsubstituted chalcones with ethylenediamine in low-polar solvents occurs along the path of attaching to the β-atom of carbon and leads to Michael bis-aza-adduct [56].

Diagram 3



However, the formation of Michael bis-aza-adducts is not the only way of the reaction proceeding. In [58] the reaction of chalcone with ethylenediamine there was obtained tetrahydrodiazepine with the 59% yield.

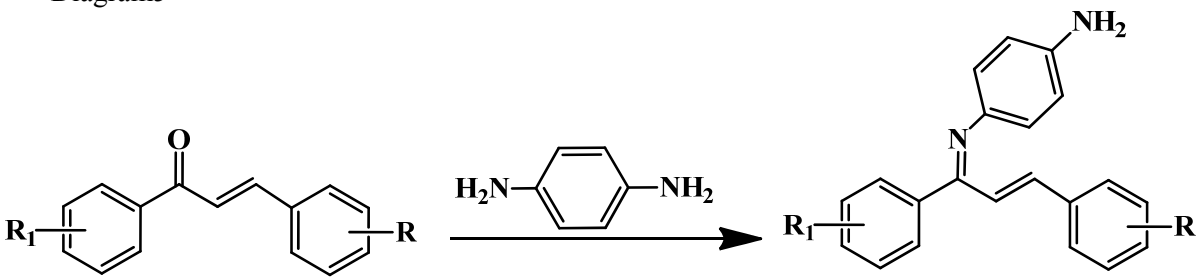
Diagram 4



The mechanism of this reaction is not described in literature, but it can be assumed that it proceeds in two stages: at first there is formed the Michael aza adduct, then there takes place its cyclization by attacking the second amino-group on the carbon atom of the carbonyl group.

The interaction of chalcons with n-phenylenediamine leads to the formation of Schiff bases that can then be used in synthesizing flavones. Synthesizing flavones and their derivatives attracts considerable attention due to their high antioxidant [60-63], anxiolytic [64], antitumor [65] and anti-inflammatory [66, 67] activity. In [68] the synthesis of iminoflavones is reported by the oxidative cyclization of chalconeimines. One of the stages of this synthesis is interaction of chalcons with substituted anilines, in particular, n-phenylenediamine, and forming the corresponding imine with a high yield. The Schiff bases that possess antibacterial activity were also obtained in [69] by the reaction of chalcones with n-phenylenediamine in water-alcohol alkali.

Diagram5

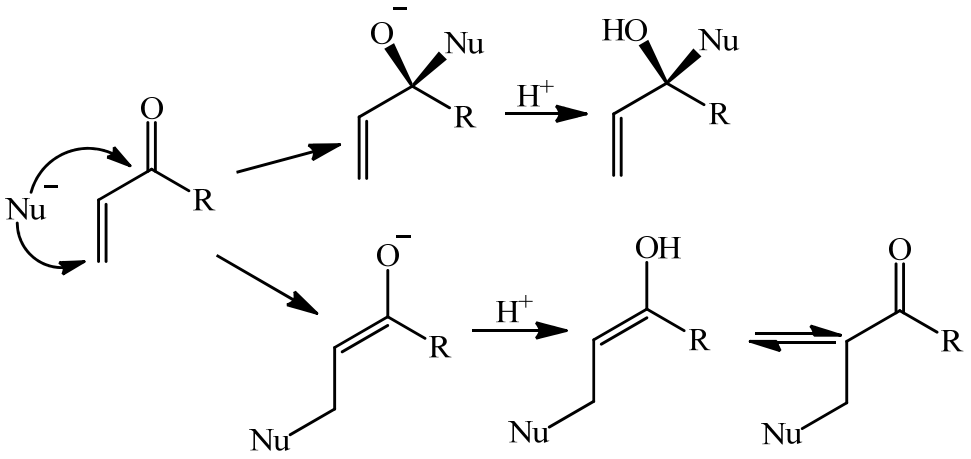


R_1=2-OH, 5-Br, R=4-OMe.
R_1=R=H, R_1=H, R=4-OMe; R_1=2-OH, R=4-NMe_2; R_1=H, R=4-NMe_2; R_1=2-OH, 5-Cl, R=4-OMe; R_1=2-OH, 5-Cl, R=H; R_1=2-OH, 5-Cl, R=4-NMe_2; R_1=2-OH, 5-Me, R=4-NMe_2.

It is known that α,β-unsaturated carbonyl compounds make it possible to synthesize practically any three-, four-, five-, six-, seven-membered carbo- and heterocycles with various substituents [1]. Therefore, chalcones are extremely popular as key intermediates in combinatorial chemistry [70]. The presence of two electrophilic centers in chalcones upon interaction with binucleophiles leads to the formation of heterocycles including annelated ones [1].

Among numerous reactions in which chalcones can participate, the interaction with binucleophilic reagents that leads to a variety of carbo- and heterocyclic compounds, in particular to substituted cyclohexanones and pyrimidines that also possess a wide spectrum of biological activity, is of particular interest.

The interaction of α,β-unsaturated carbonyl compounds (aldehydes, ketones (chalcones), acids, ethers) with nucleophiles leads to the formation of a new C-C or C-N bond. A new bond is formed between the donor and the second or fourth carbon atom of the acceptor. The first type of reaction is a simple addition via the carbonyl group, in the second case when the nucleophile is attached, the electron pair moves from the donor carbon to the acceptor oxygen.



The factors determining this process directionare charge interacting and orbital matching that are closely related to the concepts of hardness and softness of acids and bases. The interaction of a hard acid with hard bases is determined by the interaction of charges, while the reaction of a soft acid with a soft base proceeds under orbital control [71]. The relative reactivity of carbanions in the reactions of 1,2- and 1,4-addition has been considered from the standpoint of perturbation theory of molecular orbitals. Within the framework of this theory, taking into account the electronic structure of the fragment, the maximum positive effective charge on carbonyl carbon, the maximum localization of HOMO is at the β-carbon atom. The addition on the carbonyl group goes under the charge control, and 1,4-addition under the orbital control. As a consequence, all other conditions being equal, the process of nucleophile addition via the carbonyl group is favored by the charge localization at the nucleophilic center, the lowering of the HOMO energy. On the contrary, increasing the degree of the charge delocalization, increasing the HOMO level of the nucleophile promotes the flow of orbitally controlled 1,4-addition [1].

The balance between the two directions of reactions is so sensitive to various actions (solvent, catalyst, temperature) that relatively small changes are sufficient to make one of the processes dominant.

Therefore, both the advantage and the disadvantage of this reaction is the different reactivity of the nucleophilic centers, since the conditions depend not only on the structure of the reaction products, but also on their yield and purity. The development of approaches to the production of various products depending on the reaction conditions has attracted the attention of synthetics in recent years. Such processes are called "selective switch reactions". They have become widespread recently, especially for synthesizing biologically active compounds. The "switching" methods, in addition to the above-mentioned ones (solvent, catalyst, temperature), can be microwave or ultrasonic effects [72, 73].

4. Biological activity of chalcone derivatives

Compounds with the chalconic fragment show different types of biological activity. For example, they show significant activity against a variety of tumors and have chemoprotective properties. This can be attributed to their antioxidant activity [74-77]. Other important properties of chalcones are the ability to inhibit bacterial growth [78], as well as manifestation of antifungal and antiviral activity [79]. In addition, they have the ability to strengthen capillaries and can be used as anti-inflammatory agents [80]. In addition to these types of activity, they possess antimalarial [81-85], anti-cancer [86-88], larvicide [89], immunomodulating [90], antihyperglycaemic, antituberculous [91], antiprotozoal and antimitotic activity [92] and can be used as antibacterial [93, 94] and antifungal [95, 96] preparations. The inhibitory effect on enzymes, especially on the alpha-amylase of mammals [97], cyclooxygenase (COG) [98], monoamine oxidase (MAO) [99], leukotriene B [100], tyrosinase [101], aldose reductase [102], etc.

High biological activity manifested by the chalcones, promoted the development of studying the interaction of these compounds with various biological targets. There are numerous experimental data of the chalcone functions in plants, which make it possible to assert that many chalcones play an active physiological role in the plant organism. They can be relatively easily oxidized or reduced and their oxidation-reduction potential indicates that they take part in the metabolism. Some compounds of the

chalcone structure perform a protective function [95], the functions of respiratory catalysts and are involved in oxidation-reduction processes during respiration of plant cells.

The compounds with electron-donor substituents, for example, methoxy-, hydroxyl groups, show the greatest antimicrobial activity [103]. Chalcones containing one or two chlorine or fluorine atoms exhibit high antifungal and antimicrobial activity. Among the chalcones containing the oxathiolone fragment [104] there have been found compounds showing cytotoxicity against human cancer cells, as well as against *Micrococcus luteus, Staphylococcus aureus, Micobacterium tuberculosis* H Rv.

Interesting properties of chalcones also include initiation of apoptosis of cancer cells [105], inhibition of their mitochondrial respiration. The authors of [106] noted that chalcones with a smaller number of hydroxyl groups in rings A and B are more effective in this respect compared to chalcones containing more hydroxyl groups. This difference in activity is explained by the acidity of the phenolic OH groups. One of the widely known mechanisms according to which chalcones show cytotoxic activity is the interaction of chalcones in the mitosis phase. N.H. Nam with co-authors [106] studied the activity of the derivatives of 2', 5'-dihydroxychalcones and found that most chalcones exhibit cytotoxic activity against various lines of tumor cells.

Dehydroxyderivatives of chalcones show antioxidant activity that depends on the compound structure [107]. The mechanism of antioxidant activity of chalcones is discussed in [108]. When a chalcone molecule interacts with a radical, a phenoxide radical is formed with the *ortho*- and *para*-dihydroxylated systems of the benzene ring are systems with delocalized electrons, therefore the phenoxide radicals formed in them are readily converted into stable seven-quinone radicals that are further converted into quinones. *Meta*-dihydroxylated benzene ring system is less effective for electron delocalization, as a result of which phenoxide radicals are unable to enter further transformations. It has been established that chalcones with *ortho*- (i.e. 2', 3'- and 3', 4'-) and *para*- (i.e. 2', 5'-) substituents exhibit a very high antioxidant activity (80-90 % in comparison with the control at the concentration of 50 μM), which is comparable with the activity of ascorbic acid and α-tocopherol. On the other hand, chalcones with *meta*- (i.e. 2', 4'- and 3', 5'-) substituents show rather sharp decrease in activity (25% vs. control) at the concentration of 200 μM (IC_{50} >200 μM). These data show that the position of the two hydroxyl groups in the B nucleus is an important structural factor of their antiradical activity, while *para*-substituted compounds show a higher activity than the *ortho*-substituted ones. The variation of the substituents in the *para*-position in the A ring does not strongly affect the antiradical activity.This indicates that the electronic effects of the *para*-substituent of the benzene ring do not affect the antiradical activity.

The potential antioxidant activity of some hydroxychalcones was evaluated owing to their ability to inhibit 1,1-diphenyl-2-picrylhydrazyl radicals and free hydroxyl radicals [108]. For naringenin and phloretin, antiproliferative activity against the breast cancer cell line (MCF-7) has not been detected. But other chalcones (including 2'-hydroxychalcon) have shown antiproliferative activity at high concentrations (10.50 μM), and at low concentrations (0.01-1 μM) they accelerated the cell growth.

For manifesting anti-inflammatory activity of chalcones α,β-unsaturated carbonyl functional group is responsible. H.L. Yadav and co-workers [109] synthesized a series of five derivatives of chalcones and investigated their anti-inflammatory activity in rats that modeled carrageenan hind paw edema. The chalconic derivatives in the dose of 25 mg/kg fedorally, significantly inhibited the development of edema. The results of studying the anti-inflammatory activity of chalcones are also given in Ref. [50]. Activated macrophages play the key role in anti-inflammatory responses and releasing a variety of mediators, including nitric oxide (NO) that is a potential vasodilator that facilitates leukocytes migration and edema forming, as well as leukocyte activity and cytokine formation. The chalcones with substituents that increase the electron density of the Bring, for example, MeO-, BuO-, Me N-groups, do not show significant activity in inhibiting the NO production process [110].

S.J. Won et al. [111] showed that 2', 4-dihydroxychalcone, 2'-hydroxy-2-thienylchalcone, 2'-hydroxy-3-thienylchalkone and 2', 5'-dihydroxyindol-3-yl-chalcone are potential anti-inflammatory agents.

Hyperglycemic activity of chalcones was studied in [112]. Non-insulin-dependent diabetes (Type II diabetes) is a chronic metabolic disease characterized by insulin resistance, hyperglycemia and hyperinsulinemia. From *Broussonetia papyrifera* there have been isolated substituted chalcones that selectively inhibit enzymes of protein tyrosine phosphatase (PTP1B) and aldose reductase. Their

antioxidant properties allow considering them as hyperglycemic agents, because oxidative stress also plays an important role in diabetics. 3,4-dimethoxy derivatives show a significant anti-hyperglycemic effect, while monomethoxy derivatives show reduced activity.

Chlorine-containing chalcones show significant antiplasmodial activity, and chalcones with triazole, pyrrole and benzotriazole rings possess antiparasitic activity. It has beens found that the chlorine-derived chalcones with the morpholino ring possess the lowest activity. Compounds containing a triazole ring and chlorine have the greatest antiplasmodial activity, confirming the fact that small lipophilic groups containing one or more nitrogen atoms can increase antimalarial activity *in vitro*.

In vitro studies of the antiplasmoidal activity of substituted [(4-Cl, 4-MeO, 3,4,5-$(MeO)_3$] have shown that small and medium-sized lipophilic groups containing nitrogen atoms or amine in the acetophenone fragment are potential antimalarial agents. Such compounds can provide additional hydrogen bonding to the histidine residue present in the active site of the cysteine proteinase enzyme.Antileishmanial activity[113, 114]ischaracteristic of chalcones with a more hydrophilic character, that is, for HO-derivatives of chalcones, as well as for chalcones with naphthalene and pyridine fragments in the A nucleus. The inhibiting activity of tyrosinase of a number of chalcones with respect to melanin formation reactions and their antioxidant potentials has been studied [115] .The position of OH groups in aromatic A and B nuclei is very important, since hydroxylation over the B ring leads to a much higher ability to inhibit tyrasinase than hydroxylation over the A ring.

5. Conclusion

Valuable pharmacological properties of natural chalcones possessing a wide spectrum of biological action allow predicting and expanding the possibilities of developing new approaches to solving the problem of increasing biological activity of this class. By changing the structure of the chalcone molecules it is possible to increase the absolute indices of their activity in biological tests. Chalcones asα,β-unsaturated ketones are of interest as starting materials for the production of unavailable derivatives of other classes of compounds, which is due to the presence of two electrophilic centers: the carbon atom of the carbonyl group and theβ-carbon atom.

REFERENCES

[1] Desenco, S.M. Azaheterocyclesnaosnovearomaticheskichnepredelnychketonov /S.M. Desenco, V.D. Orlov. Kharkiv: Folio, **1998**. 148 p.

[2] Sahu, N.K., Balbhadra S.S., Choudhary J., Kohli D.V. Exploring pharmacological significance of chalcone scaffold: a review. // Curr.Med.Chem. **2012**. V.19. P. 209–225.

[3] AveryanovaE. V., Shkolnikov M. N., Egorova E. Yu.Physiologicheskyaktivnyeveshestvarastitelnogosyrya: uchebnoeposobie. Biysk: Alt. state. tech. un-t, **2010**. 80 p.

[4] Bondakova M.V.Razrabotka recepturyi technology roizvodstva cosmeticheskich izdelii s ispolzovaniem ecstracta vinograda: diss. ... c.t.n. M., 2014. 115 p.

[5] Sheffer-Korbilo L., Shevchik G., Du-Tyum L.Izmenenie cveta soderzhashich chalconpreparativnych form po uchodu za rotovoi polostyu. PatentRF 2524631.Zayavca: 06.01.2011. Opublicovano: 27.07.2014. Byulleten № 21.

[6] Kishore P. H., Reddy M. B., Gunasekar M., Caux C., Bodo B. Flavonoidsfrom An-drographis lineata // Phytochemistry. No. 63.P. 457-461.

[7] Logendra S., Ribnicky D. M., Yang H., Poulev A., Ma J., Kennelly E. J., Raskin I.Bioassay-guided Isolation of Aldose Reductase Inhibitors from Artemisia dracunculus // Phytochemistry. **2006**. No. 67. P. 1539-1546.

[8] Jayasinghe L., Balasooriya B. A. I. S., Padmini W. C., Hara N., Fujimoto Y.Geranyl Chalcone Derivatives with Anti-fungal and Radical Scavenging Properties from the Leavers of Artocarpus nobilis // Phytochemistry. **2004**. No. 65. P. 1287-1290.

[9] Jayasinghe L., Rupasinghe G., Hara N., Fujimoto Y.Geranylated Phenolic Constituents from the Fruits of Artocarpus nobilis // Phytochemistry. **2006**. No. 67. P. 1353-1358.

[10] Jiang C., Schommer C. K., Kim S. Y., Suh D.-Y.Cloning and Characterization of Chalcone Synthasefrom the Moss, Physcomitrella patens // Phytochemistry. **2006**. No. 67.P. 2531-2540.

[11] Meazza G., Scheffler B. E., Tellez M. R., Rimando A. M., Romagni J. G., Duke S. O., Nanayakkara D., Khan I. A., Abourashed E. A., Dayan F. E. The Inhibitory Activity of Natural Products on Plant P-hydroxyphenylpyruvate Dioxygo- nase // Phytochemistry. **2002**. No. 59. P. 281-288.

[12] Samappito S., Page J. E., Schmidt J., De-Eknamkul W., Kutchan T. M.Aromatic and Pyrone Polyketides Synthesized by a Stilbene Synthase from Rheum tataricum // Phytochemistry. 2003. No. 62. P. 313-323.

[13] Willits M G., Giovanni M., Prata R. T. N., Kramer C. M., De Luca V., Steffens J. C., Graser G.Bio-fermentation of Modified Flavonoids: an Example of in vivo Diversification of Secondary Metabolites // Phytochemistry. **2004**. No. 65. P. 31-41.

[14] Iwashina T., Kitajima J.Chalcone and Flavonol Glycosides from Asarum canadense (Aristolochiaceae) // Phytochemistry. **2000**. No. 55. P. 971-974.

[15] Tuchinda P., Reutrakul V., Claeson P., Pongprayoon U., Sematong T., Santisuk T., Taylor W. C.Anti-inflammatory Cyclohexenyl Chalcone Derivatives in Boesenbergia pandurata // Phytochemistry. **2002**. No. 59. P. 169-173.

[16] Ponce M. A., Scervino J. M., Balsells R. E., Ocampo J. A., Godeas A. M.Flavonoids from Shoots and Roots of Trifolium repens (White Clover) Grown in Presence or Absence of the Arbuscular Mycorrhizal Fungus Glomus intraradices // Phytochemistry. **2004**. No. 65. P. 1925-1930.

[17] Srinivas K V. N. S., Koteswara Rao Y., Mahender I, Das B., Rama Krishna K V. S., Hara Kishore K., Murty U. S. N. Flavonoids from Caesalpinia pulcherrima // Phytochemistry. **2003**. No. 63. P. 789-793.

[18] Ramadan M. A., Kamel M. S., Ohtani K., Kasai R., Yamasaki K. Minor Phenolics from Crinum bulbispermum Bulbs // Phytochemistry. **2000**. No. 54. P. 891-896.

[19]Реферативныйжурналхимии. **2000**. № 2. С. 208.

[20] Nookandeh A., Frank N., Steiner F., Ellinger R., Schneider B., Gerhauser C., Becker H. Xanthohumol Metabolites in Faeces of Rats // Phytochemistry. **2004**. No. 65. P. 561-570.

[21] Stevens J. F., Page J. E.Xanthohumol and Related Prenylflavonoids from Hops and Beer: to Your Good Health // Phytochemistry. **2004**. No. 65. P. 1317-1330.

[22] Martinez Valderrama J. C. Distribution of Flavonoids in the Myristicaceae // Phytochemistry. **2000**. No. 55. P. 505-511.

[23] Abe 1, Watanabe T., Noguchi H. Enzymatic Formation of Long-Chain Polyketide Pyrones by Plant Type III Polyketide Synthases // Phytochemistry. **2004**. No. 65. P. 2447-2453.

[24] Lambert S. G., Asenstorfer R. E., Williamson N. M., Hand P. G., Jones G.P. Copig-mentation between Molvidin-3-glucoside and Some Wine Constituents and Its Importance to Colour Expression in Red Wine // Food Chemistry. **2011**. No. 125. P. 106-115.

[25] Ni L., Meng C.Q., Sikorski J.A. Recent advances in therapeutic chalcones // Expert Opin.THer.Pat. **2004**. V. 14. P. 1669–1691.

[26] Herencia F. Synthesis and anti-inflammatory activity of chalcon derivatives Original Research Article / F. Herencia, M.L. Ferrandiz, A. Ubeda, J.N. Dommguez, J.E. Charris, G.M. Lobo, M.J. Alcaraz // Bioorganic and Medicinal Chemistry Letters. **1998**. V.**8**. I.10. P. 1169-1174. DOI: 10.1016/S0960-894X(98)00179-6.

[27] Sivakumar P. M. Synthesis, antimycobacterial activity evaluation, and QSAR studies of chalcone derivatives / P.M. Sivakumar, S.P. Seenivasan, V.Kumar., D. Mukesh // Bioorganic and Medicinal Chemistry Letters. **2007**. V.17. I.**6**. P. 1695-1700. DOI: 10.1016/j.bmcl.2006.12.112.

[28] Matos M.J. Potential pharmacological uses of chalcones: a patent review (from June 2011-2014) / M.J. Matos, S.V. Rodriguez, E. Uriarte, L. Santana // Expert opinion. Ther.Patents. **2014**. V. 25(3). P. 1-16. DOI: 10.1517/13543776.2014.995627.

[29] SuwitoH. Chalcones: Synthesis, structure diversity and pharmacological aspects / Hery Suwito, Jumina, Mustofa, Alfinda Novi Kristanti, Ni Nyoman Tri Puspaningsih // Journal of Chemical and Pharmaceutical Research. **2014**. V. 6(5). P. 1076-1088.

[30] Kamal, A. Synthesis and anti-cancer activity of chalcone linked imidazolones / A. Kamal,F. Ramakrishna, P. Raju, A. Viswanath, M. J. Ramaiah, G. Balakishan, M. Pal-Bhadra // Bioorganic and Medicinal Chemistry Letters. **2010**. V. 20. I. 16. P. 4865-4869. DOI: 10.1016/j.bmcl.2010.06.097.

[31]Kamal A. Solid-phase synthesis of new pyrrolobenzodiazepine-chalcone conjugates: DNA-binding affinity and anticancer activity / A. Kamal, N. Shankaraiah, S. Prabhakar, Ch. Ratna Reddy, N. Markandeya, K. Laxma Reddy, V. Devaiah // Bioorganic and Medicinal Chemistry Letters. **2008**. V. 18. I. 7. P. 2434-2439. DOI: 10.1016/j.bmcl.2008.02.047.

[32]Lopez S.N. In vitro antifungal evaluation and structure-activity relationships of new series of chalcone derivatives and synthetic analogues, with inhibitory properties against polymers of the fungal cell wall / S.N. Lopez, M.V. Castelli, S.A. Zacchino, J.N. Dominguez and etc. // Bioorganic and medicinal chemistry. **2001**. V. 9. P. 1999-2013. DOI: 10.1016/S0968-0896(01)00116-X.

[33]Rajakumar P. Photophysical properties and dye-sensitized solar cell studies on thiadiazole-triazole-chalcone dendrimers / P. Rajakumar, A. Thirunarayanan, S. Raja, S. Ganesan, P. Maruthamuthu // Tetrahedron Let. **2012**. V. 53. I. 9. P. 1139-1143. DOI: 10.1016/j.tetlet.2011.12.098.

[34] Luboch E. Bis(benzocrown ethes)s with polymethylene bridges and their application in ion-selective electrodes / E. Luboch, A. Cygan, J.F. Biernat // Tetrahedron. **1991**. V. 47. P. 4101-4112. DOI: 10.1016/S0040-4020(01)86447-4.

[35] Cibin F.R. Synthesis of ditopic cyclophane based on the cyclobutane ring by chalcone photocycloaddition / F.R. Cibin, G. Doddi, P. Mencarelli // Tetrahedron. **2003**. V. 59. P. 3455-3459. DOI: 10.1016/S0040-4020(03)00475-7.

[36] Cibin F.R. Photocycloaddition of chalcones to yield cyclobutyl ditopic cyclophanes / F.R. Cibin, N. Di Bello, G. Doddi, V. Fares, P. Mencarelli, E. Ullucci // Tetrahedron. **2003**. V. 59. P. 9971-9978. DOI: 10.1016/j.tet.2003.10.026.

[37] Rao M.L.N. Novel synthesis of macrocycles with chalcone moieties through mixed aldol reaction / M.L.N. Rao, H. Houjou, K. Hiratani // Tetrahedron Lett. **2001**. V. 42. P. 8351-8355. DOI: 10.1016/S0040-4039(01)01793-2.

[38] Gromov S.P.Molekulyarnayafotonicakraunsoderzhashichkrasitelei / S.P. Gromov // Rossiiskienanotechnologii. **2006**. T. 1. №1,2. P. 29-45.

[39] Lee J.J.Imennye Reactcii. Mechanizmyorganicheskichreakcii / J.J.Lee - Moscow: Binom. Laboratoriya znanii, **2006**. 456 p.

[40] Powers D.G. Automated parallel synthesis of chalcone-based screening libraries / D.G. Powers, D. S. Casebier, D. Fokas, W. J. Ryan, J. R. Troth, D. L. Coffen // Tetrahedron. **1998**. V. 54. P. 4085-4096. DOI: 10.1016/S0040-4020(98)00137-9.

[41] Yamin L.J. Synthesis and structure of 4-X-chalcones / L. J. Yamin, E. I. Gasull, S. E. Blanco, F. H. Ferretti // Journal of molecular structure (Theochem). **1998**. V. 428. P. 167-174. DOI: 10.1016/S0166-1280(97)00274-1.

[42] Climent M.J. Activated hydrotalcites as catalysts for the synthesis of chalcones of pharmaceutical interest / M. J. Climent, A. Corma, S. Iborra, A. Velty // Journal of catalysis. **2004**. V. 221. P. 474-482. DOI: 10.1016/j.jcat.2003.09.012.

[43] Hora L. Aldol condensation of furfural and acetone over Mg-Al layered double hydroxides and mixes oxides // L. Hora, V. Kelbichova, O. Kikhtyanin, O. Bortnovskiy, D. Kubicka // Catalysis todey. **2014**. V. 223. P. 138-147. DOI: 10.1016/j.cattod.2013.09.022.

[44] Sinisterra J.V. An improved procedure for the Claisen-Schmidt reaction / J. V. Sinisterra, A. Garcia-Raso // Synthesis. **1984**. P. 502-504. DOI: 10.1055/s-1984-30882.

[45] Petrov O. $SOCl_2$/EtOH: Catalytic system for synthesis of chalcones / O. Petrov, Y. Ivanova, M. Gerova // Catalysis Communications. **2008**. V. 9. P. 315-316. DOI: 10.1016/j.catcom.2007.06.013.

[46] Narender T.A.Simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate / T. Narender, K. Papi Reddy // Tetrahedron Lett. **2007**. V. 48. P. 3177-3180. DOI: 10.1016/j.tetlet.2007.03.054.

[47] Shen J. Bronsted acidic ionic liquids as dual catalyst and solvent for environmentally friendly synthesis of chalcone / J. Shen, H. Wang, H. Liu, Y. Sun, Zh. Liu // Journal of Molecular Catalysis A:Chemical. -**2007**. V. 280. P. 24-28.DOI: 10.1016/j.molcata. 2007.10.021.

[48] Parvulescu V. I. Catalysis in ionic liquids / V.I. Parvulescu, C. Hardacre // Chem. Rev. **2007**. V. 107. P. 2615-2665. DOI: 10.1021/cr050948h.

[49] Saravanamurugan S. Solvent free synthesis of chalcone and flavanone over zinc oxidesupported metal oxide catalysts / S. Saravanamurugan, M. Palanichamy, B. Arabindoo, V. Murugesan // Catalysis Communications. **2005**. V.**6**. P. 399-403.DOI: 10.1016/j.catcom.2005.03.005

[50] Kakati D. Microwave assisted solvent free synthesis of 1,3-diphenylpropenones / D. Kakati, J. Sarma // Chemistry central journal. **2011**. V.5(8). P. 1-5. DOI: 10.1186/1752-153X-5-8.

[51] Yanagisawa A. One-pot synthesis of 1,5-diketones catalyzed by barium isopropoxide / A. Yanagisawa, H. Takahashi, T. Arai // Tetrahedron - **2007**. V. 63. P. 8581-8585. DOI: 10.1016/j.tet.2007.04.079.

[52] Wu X. Development of general palladium-catalyzed carbonylative Heck reaction of aryl halides / X. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller // J. Am. Chem. Soc. **2010**. V. 132. P. 14596-14602. DOI: 10.1021/ja1059922

[53] Eddarir S. An efficient synthesis of chalcones based on Suzuki reaction / S. Eddarir, N. Cotelle, Y. Bakkour, C. Rolando // Tetrahedron Lett. **2003**. V. 44. P. 5359-5363. DOI: 10.1016/S0040-4039(03)01140-7

[54] Deshmukh M.B. Synthesis of dibenzo-18-crown-6 ether containing pyrimidine derivatives / M.B. Deshmukh, K.N. Alasundkar, S.M. Salunkhe, D.K. Salunkhe, S.A. Sankpal, D.R. Patil, P.V. Anbhule // Indian Journal of Chemistry. **2008**. V. 47B. P. 1915-1917.

[55] Stewart V.E., Pollard C.B. Derivatives of piperazine. IX. Addition to conjugate systems. I // J. Am. Chem. Soc. **1936**. Vol. 58. № 10. P. 1980-1981.

[56] Hideg K., Lloyd D. Reaction products from α,β-unsaturated ketones and aliphatic diamines or ditiols // J. Chem. Soc. C. **1971**. P. 3441-3445.

[57] Bandyopadhyay D., Mukherjee S., Turrubiartes L.C., Banik B.K. Ultrasound- assisted aza-Michael reaction in water: A green procedure // Ultrasonics Sonochem. **2012**. Vol. 19. P. 969-973.

[58] Zhelyazkov L., Bizhev A. Diazepine derivatives with probable pharmacological activity // Godishnik na Visshiya Khimikotekhnologicheski Institut. Sofiya. **1974**. Vol. 20. № 1. P. 251-258.

[59] Lloyd D., Scheibelein W., Hideg K. Further studies of the mixture obtained from reactions between conjugated enones and ethylenediamine, and from conjugated enones and 1-aminopropane // J. Chem. Res. (S). **1981**. P. 62-63.

[60] Rice-Evans C.A., Miller N.J., Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids // Free Radical Biol. Med. **1996**. Vol. 20. № 7. P. 933956.

[61] Rice-Evans C.A. Flavonoid antioxidants // Curr. Med. Chem. **2001**. Vol. 8. № 7. P. 797-807.

[62] Pietta P.G. Flavonoids as antioxidants // J. Nat. Prod. **2000**. Vol. 63. № 7. P. 1035-1042.

[63] Chan E.C., Patchareewan P., Owen L.W.J. Relaxation to flavones and flavonols in rat isolated thoracic aorta: mechanism of action and structure-activity relationships // Cardiovasc. Pharmacol. **2000**. Vol. 35. № 2. P. 326-333.

[64] Zanoli P., Avallone R., Baraldi M. Behavioral characterisation of the flavonoids apigenin and chrysin // Fitoterapia - **2000**. Vol. 71. № 1. P. 117-123.

[65] Liu Y.I., Ho D.K., Cassady J.M., Cook V.M., Baird W.M. Isolation of potential cancer chemopreventive agents from *Eriodictyon californicum* // J. Nat. Prod. **1992**. Vol. № 13. P. 357-363.

[66] Fishkin R.J., Winslow J.T. Endotoxin-induced reduction of social investigation by mice: interaction with amphetamine and anti-inflammatory drugs // Psychopharmacology. **1997**. Vol. 132. № 4. P. 335-341.

[67] Dao T.T., Chi Y.S., Kim J., Kim H.P., Kim S., Park H. Synthesis and inhibitory activity against COX-2 catalyzed prostaglandin production of chrysin derivatives // Bioorg. Med. Chem. Lett. **2004**. Vol. 14. № 5. P. 1165-1167.

[68] Patil S.G., Utale P.S., Gholse S.B., Thakur S.D., Pande S.V. Synthesis, characterization and antimicrobial activity of 6-bromo-4-methoxy-4-(substituted phenyl) iminoflavone // J. Chem. Pharm. Res. **2012**. Vol. 4. № 1. P. 501-507.

[69] Kedar R.M. Synthesis and antimicrobial activity of new Schiff bases // Oriental J. Chem. 2000. Vol. 16. № 2. P. 335-338.

[70] Marzinzik A.L. Key Intermediates in Combinatorial Chemistry: Access to Various Heterocycles from a,y5-Unsaturated Ketones on the Solid Phase / A. L. Marzinzik, E. R. Felder // J. Org. Chem. **1998**. V. 63. P. 723-727. DOI: 10.1021/jo971620u

[71] Laszlo P. Logica organicheskogo synteza. M.: Mir, **1998**. T.1. 229 p.

[72] Chebanov V.A. Switchable multicomponent heterocyclizations for diversity oriented synthesis / V.A. Chebanov, S.M. Desenko // Diversity Oriented Synth. **2014**. V. 1. P. 43-63. DOI: 10.2478/dos-2014-0003

[73] Chebanov V.A. Multicomponent heterocyclization reactions with controlled selectivity / V.A. Chebanov, S.M. Desenko // Chemistry of Heterocyclic Compounds. **2012**. V. 48. N. 4. - P. 566-568. DOI: 10.1007/s10593-012-1030-2

[74] Miranda C.L., Aponso G.L.M., Stevens J.F., DeinzerM.L.,BuhlerD.R.Antioxidantandprooxidantactionofpre- nylated and nonprenylated chalcones and flavanones in vitro // *J. Agric. Food Chem.* **2000**. № 48. P.3876–3884.

[75] Sivakumar P.M., Prabhakar P.K., Doble M. Synthesis, antioxidant evaluation and quantitative structureactivity relationship studies of chalcones // *Med. Chem. Res*. **2011**. Vol. 20. № 4. P.482–492.

[76] Vasil'ev R.F., Kancheva V.D., Fedorova G.F., Batovska D.I., Trofimov A.V. Antioxidant activity of chalcones: The chemiluminescence determination of the reactivity and the quantum chemical calculation of the energies and structures of reagents and intermediates // *Kinetics and Catalysis*. **2010**. Vol. 51. № 4. P.507–515.

[77] Vogel S., Ohmayer S., Brunner G., Heilmann J. Natu- ral and non-natural prenylated chalcones: Synthesis, cytotoxicity and antioxidative activity // *Bioorg. Med. Chem.* **2008**. Vol. 16. № 8. P.4286–4293.

[78] Tiwari K.N., Monserrat J.-P., Arnaud Hequet A., Ganem-Elbaz C., Cresteil T., Jaouen G., Vessières A., Hil- lard E.A. Jolivalt C. In vitro inhibitory properties of ferrocene- substituted chalcones and aurones on bacterial and human cell cultures // *Dalton Trans.* 2012. Vol. 41. P.6451–6457.

[79] DaoT.T.,NguyenP.H.,LeeH.S.,KimE.,ParkJ.,LimS., OhW.K.ChalconesasnovelinfluenzaA(H1N1)neuraminidase inhibitorsfromGlycyrrhizainflate // *Bioorg.Med.Chem.Lett*. **2011**. Vol. 21. № 1. P.294–298.

[80] Hsieh H.K., Tsao L.T., Wang J.P. Synthesis and antiinflammatory effect of chalcones // *J. Pharm. Pharmacol*. **2000**. Vol. 52. № 2. P.163–171.

[81] Awasthi S.K., Mishra N., Kumar B., Sharma M., Bhattacharya A., Mishra L.C., Bhasin V.K. Potent antimalarial activity of newly synthesized substituted chalcone analogs in vitro // *Med. Chem. Res.* **2009**. Vol. 18. № 6. P.407–420.

[82] ChengM.S.,ShiliR.,KenyonG.Asolidphasesynthesis of chalcones by Claisen-Schmidt condensations // *Chinese Chem. Lett*. **2000**. Vol. 11. P.851–854.

[83] Lim S.S., Kim H.S., Lee D.U. In vitro antimalarial activity of flavonoids and chalcones // *Bull. Korean Chem. Soc.* **2007**. Vol. 28. P.2495–2497.

[84] Liu M., Wilairat P., Go L.M. Antimalarial alkoxylated and hydroxylated chalcones: structure-activity relationshipanalysis // *J. Med. Chem*. **2001**. Vol.44. P.4443–4452.

[85] Motta L.F., Gaudio A.C., Takahata Y. Quantitative structure–activity relationships of a series of chalcone derivatives (1,3-diphenyl-2-propen-1-one) as anti-plasmodium falciparum agents (anti-malaria agents) // *Int. Electronic J. Mol. Des.* **2006**. Vol. 5. № 12. P.555–569.

[86] Achanta G., Modzelewska A., Feng L., Khan S.R., Huang P.A. A boronicchalcone derivative exhibits potent anticancer activity through inhibition of the proteasome // *Mol. Pharmacol.* **2006**. Vol. 70. P.426–433.

[87] Echeverria C., Santibanez J.F., Donoso-Tauda O., Escobar C.A., Tagle R.R. Structural Antitumoral Activity Relationships of Synthetic Chalcones **//** *Int. J. Mol. Sci.* **2009**. Vol. 10. № 1. P.221–231.

[88] Romagnoli R, Baraldi P.G, Carrion M.D, Cara C.L., Cruz-Lopez O., Preti D. Design, synthesis, and biological evaluation of thiophene analogues of chalcones // *Bioorg. Med. Chem.* **2008**. Vol. 16. № 10. P. 5367–5376.

[89] Begum N.A., Roy N., Laskar R.A., Roy K. Mosquito larvicidal studies of some chalcone analogues and their derived products: structure–activity relationship analysis // *Med. Chem. Res.* **2011**. Vol. 20. № 2. P.184–191.

[90] Barford L., Kemp K., Hansen M., Kharazmi A. Chalcones from Chinese liquorice inhibit proliferation of T cells and production of cytokines // *Int. Immunopharmacol*. **2002**. Vol. 2. P.545–550.

[91] Satyanarayama M., Tiwari P., Tripathi K., Srivastava A.K., Pratap R. Synthesis and antihyperglycemic activity of chalcone based aryloxypropanolamines// *Bioorg. Med. Chem*. **2004**. Vol. 12. № 5. P.883–889.

[92] Lunardi F., Guzela M., Rodrigues A.T., Corre R., Eger- Mangrich I., Steindel M., Grisard E.C., Assreuy J., Calixto J.B., Santos A.R. Trypanocidal and leishmanicidal properties of substitution-containing chalcones // *Antimicrobial Agents and Chemotherap*. **2003**. Vol. 47. P.1449–1451.

[93] BhatiaN.M.,MahadikK.R.,BhatiaM.S.QSARanalysis of 1,3-diaryl-2-propen-1-ones and their indole analogs for designing potent antibacterial agents // *Chem. Papers*. **2009**. Vol. 63. № 4. P.456–463.

[94] Hamdi N., Fischmeister C., Puerta M.C., Valerga P. A rapid access to new coumarinyl chalcone and substituted chromeno[4,3-c]pyrazol-4(1*H*)-ones and their antibacterial and DPPHradicalscavengingactivities//*Med.Chem.Res.* **2011**. Vol. 20. № 4. P.522–530.

[95] Bag S., Ramar S., Degani M.S. Synthesis and biological evaluation of α, β-unsaturated ketone as potential antifungal agents//*Med.Chem.Res.* **2009**. Vol.18. № 4. P. 309–316.

[96] Lahtchev K.L., Batovska D.I., Parushev S.P., Ubiyvovk V.M., Sibirny A.A. Antifungal activity of chalcones: A mechanistic study using various yeast strains // *Eur. J. Med. Chem.* **2008**. Vol. 43. № 10. P.2220–2228.

[97] Najafian M., Ebrahim-Habibi A., Hezareh N., Yaghmaei P., Parivar K., Larijani B. Trans-chalcone: a novel small molecule inhibitor of mammalian alpha-amylase // *Mol. Biol. Rep.* **2010**. Vol. 10. P.271–274.

[98] Zarghi A., Zebardast T., Hakimion F., Shirazi F.H., Rao P.N.P., Knaus E.E. Synthesis and biological evaluation of 1, 3-diphenylprop-2-en-1-ones possessing a methanesulfonamido or an azido pharmacophore as cyclooxygenase-1/-2 inhibitors // *Bioorg. Med. Chem.* **2006**. Vol. 14. № 20. P.7044–7050.

[99] Chimenti F., Fioravanti R., Bolasco A., Chimenti P., SecciD.,RossiF.,YanezM.,FranciscoO.F.,OrtusoF.,AlcaroS. Chalcones:avalidscaffoldformonoamineoxidasesinhibitors// *J. Med. Chem.* **2009**. Vol.49. № 16. P.4912–4925.

[100] Deshpande A.M., Argade N.P., Natu A.A. Synthesis and screening of a combinatorial library of naphthalene substituted chalcones inhibitors of leukotriene B4 // *Bioorg. Med. Chem.* **1999**. Vol. 7. № 6. – P.1237–1240.

[101] Khatib S., Nerua O., Musa R., Shmnell M., Tamir S., VayaJ.Chalconesaspotenttyrosinaseinhibitors:theimportance of a 2,4-substituted resorcinol moiety // *Bioorg. Med. Chem*. **2005**. Vol. 13. № 2. P.433–441.

[102] Severi F., Benvenu S., Constantino L., Vampa G., Melegari M., Antolini L. Synthesis and activity of a new series of chalcones as aldose reductase inhibitors // *Eur. J. Med. Chem.* **1998**. Vol. 33. № 11. P. 859–866.

[103] Konieczny M.T., Konieczny W., Sabisz M., Skladanowski A., Wakieć R., Augustynowicz-Kopeć E., Zwolska Z. Acid-catalyzed synthesis of oxathiolone fused chalcones. Comparisonoftheiractivitytowardvariousmicroorganismsand humancancercellsline//*Eur.J.Med.Chem*. **2007**. Vol.42. № 5. P. 729–733.

[104] Reddy M.V.B., Su Ch.R, CHiou W.I., Lee K.H., Wua T.S. Design, synthesis, and biological evaluation of Mannichbasesofheterocyclicchalconeanalogsascytotoxicagents// *Bioorg. Med. Chem*. **2008**. Vol. 16. № 15. P.7358–7380.

[105] Sabzevarib O., Galati G., Moridani M.Y., Siraki A., O'Brien P.J. Molecular cytotoxic mechanisms of anticancer hydroxychalcones // *Chem-Biol. Interactions*. **2004**. Vol. 148. № 1–2. P. 57–67.

[106] Nam N.H., Kim Y., You Y.J., Hong D.H., Kim H.M., Ahn B.Z. Cytotoxic 2′,5′-dihydroxychalcones with unexpected antiangiogenicactivity//*Eur. J.Med.Chem*. **2003**. Vol.38. № 2. P. 179–187.

[107] Beom-Tae Kim, Kwang-Zoong O., Jae-Chul Chun, Ki-Jun Hwang. Synthesis of dihydroxylated chalcone derivatives with diverse substitution patterns and their radical scavenging ability toward DPPH free radicals // *Bull. Korean. Chem. Soc*. **2008**. Vol. 29. № 6. P.1125–1130.

[108] CallisteC.A.,LeBailJ.C.,TrouilasP.,PougetC.,Habrioux G., Chulia A.J. Chalcones: structural requirements for antioxidant,estrogenicandantiproliferativeactivities.//*Anticancer Res*. **2001**. Vol. 21. № 6A. P.3949–3956.

[109]Yadav H.L., Gupta P.,Pawar P.S., Singour P.K., Patil U.K. Synthesis and biological evaluation of anti-inflammatory activity of 1,3-diphenylpropenone derivatives // *Med. Chem. Res.* **2010**. Vol. 19. № 1. P.1–8.

[110] Rojas J., Dominguez M.P.J.N., Ferrándiz M.L. The synthesis and effect of fluorinated chalcone derivatives on nitric oxideproduction//*Bioorg.Med.Chem.Lett*. **2002**. Vol.12. № 15. P. 1951–1954.

[111] Won S.J., Liu C.T., Tsao L.T., Weng J.R., Ko H.H., Wang J.P., Lin C.N. Synthetic chalcones as potential anti-inflammatory and cancer chemopreventive agents // *Eur. J. Med. Chem*. **2005**. Vol. 40. № 1. P. 103–112.

[112] AndersonA.Ahydroxychalconederivedfromcinnamon functionsasamimeticforinsulinin3T3-L1adipocytes//*J.Am. Coll Nutr*. **2001**. Vol. 20. № 4. P.327–336.

[113] Jun N., Hong G., Jun K. Synthesis and evaluation of 2′,4′,6′-trihydroxychalcones as a new class of tyrosinase inhibitors // *Bioorg. Med. Chem*. **2007**. Vol. 15. № 6. P. 2396–2402.

[114] Liu M., Wiliarat P., Croft S.L. Structure activity relationships of antileishmanial and antimalarial chalcones // *Bioorg. Med. Chem.* **2003**. Vol. 11. № 13. P.2729–2738.

[115] Meng C.Q., Zheng X.S., Ni L., Ye Z., Simpson J.E., Worsencroft K.J., Hotema M. R., Weingarten M. D., Skudlarek J.W., Gilmore J.M., Hoong L.K., Hill R.R., Marino E.M., Suen K.L., Kunsch C., Wasserman M. A., Sikorski J. A. Discovery of novel heteroarylsubstituted chalcones as inhibitors of TNF-R-induced VCAM-1 expression // *Bioorg. Med. Chem. Lett*. **2004**. Vol. 14. № 6. P.1513–1517.

ӘОЖ 577.127:547.973

О.А. Нуркенов[1,2], М.К. Ибраев[2], С.Д. Фазылов[1], А.Т. Такибаева[2], И.В. Кулаков[3], А.Е. Туктыбаева[2]

[1] Қазақстан Республикасының органикалық синтез және көмірхимия институты, Қарағанды, Қазақстан;
[2]Қарағанды мемлекеттік техникалық университеті, Қарағанды, Қазақстан;
[3]Ф.М.Достоевский атындағы Омск мемлекеттік университеті, Омск, Ресей

ХАЛКОНДАР–БИОЛОГИЯЛЫҚ БЕЛСЕНДІ ЗАТТАР СИНТЕЗІНДЕГІ СИНТОНДАР

Аннотация:бұл шолу мақаласында соңғы жылдардағы әдеби мәліметтер, сондай-ақ функционалды орынбасқан халкондароблысындағы авторлардың зерттеулер нәтижелері жинақталып, жүйеленген. Кең таралған табиғи халкондар, синтетикалық халкондардың алу әдістері, реакциялық қабілеті мен биологиялық қасиеттері келтірілге.

Түйін сөздер: орынбасқан ароматты альдегид, халкон, пиразолин, флавонон, цитокин, транскрипционды фактор NF-κB

О.А. Нуркенов[1,2], М.К. Ибраев[2], С.Д. Фазылов[1], И.В. Кулаков[3], А.Т. Такибаева[2], А.Е. Туктыбаева[2]

[1]Институт органического синтеза и углехимии Республики Казахстан, Караганда, Казахстан;
[2]Карагандинский государственный технический университет, Караганда, Казахстан;
[3]Омский государственный университет им. Ф.М. Достоевского, Омск, Россия

ХАЛКОНЫ - СИНТОНЫ В СИНТЕЗЕ БИОЛОГИЧЕСКИ АКТИВНЫХ ВЕЩЕСТВ

Аннотация: в обзорной статье обобщены и систематизированы литературные данные последних годов, а также результаты исследований авторов в области функционально замещенных халконов. Приведены наиболее распространённые природные халконы, методы получения, реакционная способность и биологические свойства синтетических халконов.

Ключевые слова: замещенный ароматический альдегид, халкон, пиразолин, флавонон, цитокин, транскрипционный фактор NF-κB.

МАЗМҰНЫ

* * *

СОДЕРЖАНИЕ

CONTENTS

* * *

Publication Ethics and Publication Malpractice in the journals of the National Academy of Sciences of the Republic of Kazakhstan

For information on Ethics in publishing and Ethical guidelines for journal publication see http://www.elsevier.com/publishingethics and http://www.elsevier.com/journal-authors/ethics.

Submission of an article to the National Academy of Sciences of the Republic of Kazakhstan implies that the described work has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see http://www.elsevier.com/postingpolicy), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. In particular, translations into English of papers already published in another language are not accepted.

No other forms of scientific misconduct are allowed, such as plagiarism, falsification, fraudulent data, incorrect interpretation of other works, incorrect citations, etc. The National Academy of Sciences of the Republic of Kazakhstan follows the Code of Conduct of the Committee on Publication Ethics (COPE), and follows the COPE Flowcharts for Resolving Cases of Suspected Misconduct (http://publicationethics.org/files/u2/New_Code.pdf). To verify originality, your article may be checked by the Cross Check originality detection service http://www.elsevier.com/editors/plagdetect.

The authors are obliged to participate in peer review process and be ready to provide corrections, clarifications, retractions and apologies when needed. All authors of a paper should have significantly contributed to the research.

The reviewers should provide objective judgments and should point out relevant published works which are not yet cited. Reviewed articles should be treated confidentially. The reviewers will be chosen in such a way that there is no conflict of interests with respect to the research, the authors and/or the research funders.

The editors have complete responsibility and authority to reject or accept a paper, and they will only accept a paper when reasonably certain. They will preserve anonymity of reviewers and promote publication of corrections, clarifications, retractions and apologies when needed. The acceptance of a paper automatically implies the copyright transfer to the National Academy of Sciences of the Republic of Kazakhstan.

The Editorial Board of the National Academy of Sciences of the Republic of Kazakhstan will monitor and safeguard publishing ethics.

Правила оформления статьи для публикации
в журнале смотреть на сайте:

www:nauka-nanrk.kz

http://www.chemistry-technology.kz/index.php/ru/

ISSN 2518-1491 (Online), ISSN 2224-5286 (Print)

Редакторы: *М. С. Ахметова, Т. А. Апендиев, Аленов Д.С.*
Верстка на компьютере *А.М. Кульгинбаевой*

Подписано в печать 04.08.2018.
Формат 60x881/8. Бумага офсетная. Печать – ризограф.
11,5 п.л. Тираж 300. Заказ 4.

Национальная академия наук РК
050010, Алматы, ул. Шевченко, 28, т. 272-13-18, 272-13-19