DOI 10.31489/2019Ch3/28-36

UDC 577.127:547.973

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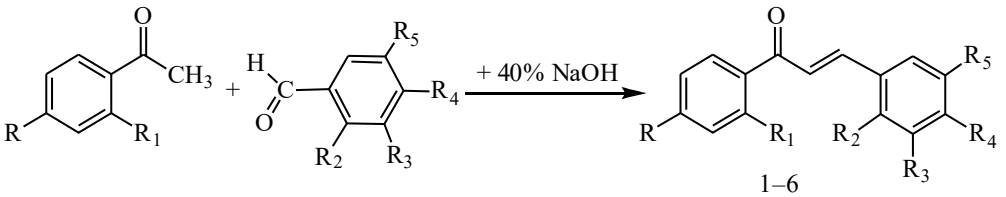
Synthesis, structure and antimicrobial activity of substituted chalcones and their derivatives

In the paper the interaction reactions of the hydroxyl substituted acetophenones with the substituted aromatic aldehydes in the presence of aqueous alcoholic solution of alkali (Claisen-Schmidt condensation), which is as aldol condensation were given. This reaction has a big duration and comes to the end within 62–85 h. The final product contains double bonds in α,β-position to carbonyl group. Further functionalization of the chalcones obtained was performed by their correlation with hydrazine hydrate. It was found that boiling of chalcones with hydrazine hydrate in ethanol led to an intramolecular cyclocondensation of an intermediate hydrazone to form some pyrazole derivatives. Structures of the synthesized compounds were studied with ^{1}H and ^{13}C-NMR spectroscopy, and data on two-dimensional (^{1}H-^{1}H) COSY and (^{1}H-^{13}C) HMQC spectra. Values of the chemical shifts, multiplicity and integral intensity of signals in one-dimensional ^{1}H and ^{13}C NMR spectra were determined. Homo- and heteronuclear interactions confirming structure of the compounds studied were determined with (^{1}H-^{1}H) COSY and (^{1}H-^{13}C) HMQC spectra. Data on the antimicrobial activity of the synthesized chalcones, pyrazolines and flavonones were showed. It was found that all studied substances practically showed a weak antibacterial activity. Exception is S. aureus culture, which possess the moderate actions for compounds of (E)-1.3-bis (2-hydroxyphenyl)-prop-2-en-1-one, (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)-prop-2-en-1-one,(E)-3-(ethoxy-4-hydroxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one and 2-(2-hydroxyphenyl)flavone.

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

Chalcones are of a considerable interest caused with their easy synthesis, high pharmacological activity and possibility of application as synthon in synthesis of many biologically active heterocyclic compounds, in particular, pyrazolines and flavones. Compounds with chalcone fragment have the high antitumoral, antibacterial, antifungal, antivirus, antimalarial, anti-hyperglycemic, anti-inflammatory and immunomodulatory activities, and demonstrate the chemoprotective and antioxidant properties [1–11]. In addition some chalcone derivatives have an ability to strengthen capillaries [5]. The traditional methods of obtaining chalcones provide the using as catalysts of such strong bases as hydroxides of alkaline and alkaline-earth metals [12]. In this connection the synthesis of new chalcones and nitrogen-containing heterocyclic compounds on their basis is represented an important object.

This paper studied the interaction reactions of the hydroxyl substituted of acetophenones with the substituted aromatic aldehydes in the presence of aqueous alcoholic solution of alkali (Claisen-Schmidt condensation) which was as aldol condensation. The reaction mixture was mixed with a magnetic stirrer at room temperature; reaction has a big duration and comes to the end within 62–85 h. The final product contains double bonds in α,β-position to carbonyl group. The chalcones obtained (1–6) are yellow or orange powders, dissoluble in benzene and alcohol.

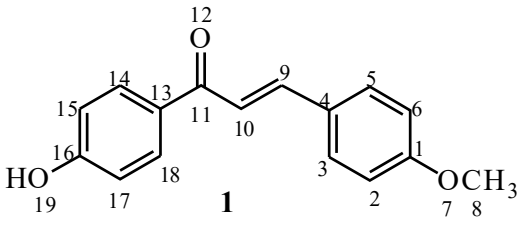


1–6

R = HO; R_1 = H; R_4 = CH_3O; R_2 = R_3 = R_5 = H (1).
R = H; R_1 = HO; R_2 = HO; R_3 = R_4 = R_5 = H (2).
R = HO; R_1 = HO; R_4 = CH_3O; R_2 = R_3 = R_5 = H (3).
R = H; R_1 = HO; R_2 = R_3 = R_5 = H; R_4 = HO (4).
R = H; R_1 = HO; R_2 = R_5 = H; R_3 = C_2H_5O; R_4 = HO (5).
R = Br; R_1 = H; R_2 = HO; R_3 = R_4 = H; R_5 = Br (6).

The structure of the chalcones synthesized (1–6) was proved with IR- and ^{1}H, ^{13}C NMR spectroscopy.

IR spectrum of chalcones (1–6) demonstrates intense absorption bands at 1595–1582 cm^{-1} that correspond to vibrations of C=C bond attached to a carbonyl group.



1

^{1}H NMR spectrum of compound 1 in deuterated DMSO shows the high intense singlet signal with a chemical shift (3.76 ppm) and intensity of 3H belonging to protons of OCH_3[8] methoxy-group. Equivalent protons of methoxyphenyl fragment of $H^{2.6}$ and $H^{3.5}$ were resonated with doublet signals at 6.95 (2H, ^{3}J 8.5 Hz) and 7.77 ppm (2H, ^{3}J 8.6 Hz), respectively. Protons at double bond of H^{9} and H^{10} give doublet signals at 7.74 and 7.62 ppm with intensity of 1H with splitting of ^{3}J 17.1 and 15.3 Hz, respectively. The equivalent CH-protons of group of other aromatic system were shown with doublet signals with intensity of 2H at 6.86 ($H^{15.17}$, ^{3}J 9.2 Hz) and 8.03 ppm ($H^{14.18}$, ^{3}J 8.5 Hz). A broadened singlet signal at 10.39 ppm demonstrated the phenolic hydroxyl in compound.

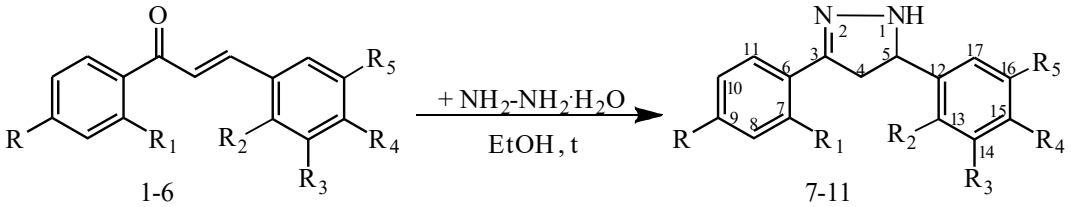
^{13}C NMR spectrum of the studied compound 1 shows a signal of methoxy group at 55.83 ppm. Carbon atoms of the aromatic systems give signals at 114.87 ($C^{2.6}$), 115.88 ($C^{15.17}$), 131.05 ($C^{3.5}$) and 131.57 ppm ($C^{14.18}$). Signals with the chemical shifts of 161.62 (C^{1}), 128.04 (C^{4}), 129.84 (C^{13}), and 162.61 (C^{16}) ppm correspond to quarternary carbon atoms. Signals at 120.08 and 143.21 ppm include the carbon atoms connected by a multiple bond of C^{9} and C^{10} respectively. A weak-field signal at 187.57 ppm corresponds to C^{11} atom of carbonyl group.

The structure of compound (1) was confirmed by two-dimensional NMR, ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMQC spectroscopy for definition of the spin-spin coupling of homo-and heteronuclear nature.

^{1}H-^{1}H COSY spectra of compound 1 demonstrate the spin-spin correlations through three bonds of protons of aromatic systems and olefinic protons of H^{9} and H^{10}. Simple correlations of protons with carbon atoms were determined by ^{1}H-^{13}C HMQC spectroscopy.

Reaction of cyclocondensation of hydrazines with α,β-unsaturated ketones is an important synthetic way to 1.2 azoles. Some pyrazole derivatives show properties of analgetics and inhibitors of thrombocyte aggregation [13], possess the strong antibacterial [14] and anesthetized [15] actions.

In order to determine functions of the chalcones (1–6) obtained their correlation with hydrazine hydrate was studied. It was found that boiling of chalcones with hydrazine hydrate in ethanol led to an intramolecular cyclocondensation of an intermediate hydrazone to formation of pyrazole derivatives (7–11).

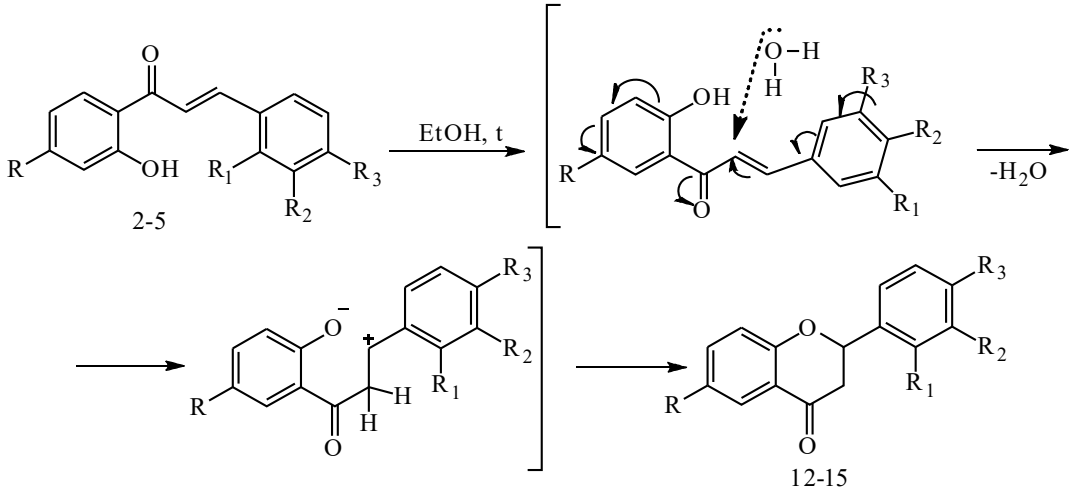


R = HO; R_1 = H; R_4 = CH_3O; R_2 = R_3 = R_5 = H (7).
R = H; R_1 = HO; R_2 = HO; R_3 = R_4 = R_5 = H (8).
R = HO; R_1 = HO; R_4 = CH_3O; R_2 = R_3 = R_5 = H (9).
R = H; R_1 = HO; R_2 = R_3 = R_5 = H; R_4 = HO (10).
R = H; R_1 = HO; R_2 = R_5 = H; R_3 = C_2H_5O; R_4 = HO (11).

The structure of compounds (7–11) was confirmed by IR and NMR spectroscopy. Thus, IR spectra of pyrazolines (7–11) demonstrate a strip of average intensity of C=N group of pyrazoline core at 1601–1605 cm^{-1}.

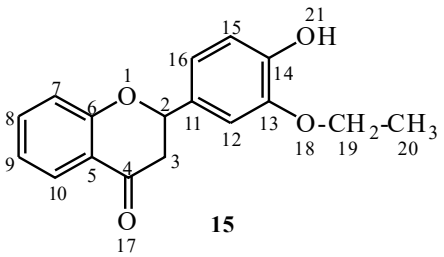
^{1}H NMR spectrum of 4-(5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-3-il)phenol (**7**) established that four groups of signals in the low field corresponded to protons of 4-hydroxy- and 4-methoxyphenyl fragments. Two doublets at 7.40 and 7.23 ppm correspond to *ortho*- and *meta*-protons of 4- hydroxyphenyl fragment and two doublets at 6.84 and 6.72 ppm — *ortho*- and *meta*-protons of a 4-methoxyphenyl fragment. Protons of methoxy-group correspond to an intense singlet at 3.67 ppm. The following group of signals representing a triplet at 4.63–4.68 ppm is relevant to a methine proton (CH_{pyr}) of pyrazoline fragment. Methylene protons of this fragment resonate at 2.65–2.72 ppm as two doublets. A weak signal at 9.67 ppm belongs to NH proton of a pyrazoline fragment.

Combination of the structural features of these compounds in one molecule to obtain highly effective biologically active substances is of interest in view of generality of some biogenesis processes of chalcones and flavonoids in a vegetable organism [16, 17]. In connection with this, flavonones (12–15) were obtained from synthesized 2-hydroxyl-containing chalcones under ethanol and catalytic amounts of triethylamine. Long boiling in 95 % ethanol leads to isomerization of chalcones (2–5) into flavonones (12–15). It is demonstrated that isomerization process of chalcones into flavonones in alcohol is catalyzed by water molecules.



R = H; R_1 = HO; R_2 = R_3 = H (12).
R = HO; R_1 = R_2 = H; R_3 = CH_3O (13).
R = R_1 = R_2 = H; R_3 = HO (14).
R = H; R_1 = H; R_2 = C_2H_5O; R_3 = HO (15).

The structure of flavonones (12–15) was proved by IR- and ^{1}H, ^{13}C NMR spectroscopy. Thus, a triplet signal with a center of 1.29 ppm and multiplet at 3.98–4.03 ppm belong to protons of ethoxy-group at C^{20} and C^{19} in ^{1}H NMR spectrum of flavonone 15. Protons of methylene- and CH-groups of the system of condensed cores are shown in a spectrum area: H^2 at 5.47, H^3 — 2.69–3.31, H^7 — 7.06, H^8 — 7.55, H^9 — 7.76 and H^{10} — 7.04 ppm. Resonating at 6.77–6.90 ppm is characteristic for CH-groups of a phenyl radical. A weak pole at 9.00 ppm demonstrates a signal H^{21} of hydroxyl group.



15

Interpretation of DEPT spectra permitted to correlate eight signals of carbon spectrum with methine groups; two signals with methylene groups and one signal with methyl group. The detailed analysis of ^{13}C NMR of compound (15) showed that a signal at 15:29 ppm corresponded to CH_3-group at C^{20} atom. CH_2-groups appear at 44.03 (C^3) and 64.55 (C^{19}) ppm. Eight signals of CH-groups resonate at 79.57 (C^2), 113.10 (C^{12}), 115.86 (C^{15}), 118.57 (C^7), 120.20 (C^{16}), 121.81 (C^9), 128.81 (C^{10}) and 136.71 (C^8) ppm. An additional point is that ^{13}C NMR spectrum shows signals at 121.15, 130.18, 147.20, 147.77 and 161.76 ppm, which belong to C^5, C^{11}, C^{14}, C^{13} and C^6 atoms, respectively. A low field signal at 192.47 ppm belongs to a carbonyl C^4 atom.

Three chalcones (2, 4, 5), two pyrazolines (8, 9) and two flavones (12, 14) were investigated to estimate their antimicrobical activity for the medicinal and sensitive museum strains of bacteria and fungi.

A microbiological laboratory to test the antibacterial and antifungal activities on the basis of Department of Microbiology at Karaganda Medical University studied the synthesized compounds on antimicrobical activity of some drugs such as (E)-1,3-bis(2- hydroxyphenyl)-prop-2-en-1-one (2), (E)-1-(2-hydroxyphenyl)-3-(4-hydroxy-phenyl)-prop-2-en-1-one (4), (E)-3-(ethoxy-4-hydroxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-

1-one (5), 2,2-(4,5-dihydro-1H-pyrazole-3,5-diil)phenol (8), 4-(5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-3-il)benzol-1,3-diol (9), 2-(2-hydroxyphenyl)flavone-4-one (12), 2-(4-hydroxyphenyl)flavone-4-one (14).

Concentrations of the tested drugs were made for an antibacterial activity, namely 1 μg and antifungal — 1 μg. Concentration of reference substances made 1 mg. The antimicrobical activity of samples was estimated on diameter of zones of a growth inhibition of test strains (mm). Diameters of zones less than 10 mm and the continuous growth in dish were estimated as lack of an antimicrobical activity, and 10–15 mm — weak activity, 15–20 mm — moderate activity and over 20 mm — an expressed antimicrobical activity. Each sample was tested in three parallel studies.

The statistical processing was performed by methods of the parametrical statistics with calculation of the average arithmetic and standard errors.

Dilution was made at 1 mg of substance per 1 ml of solvent. Bacteria sensitivity to these substances was determined by a diffusive method with disks. Bacteria such as *S. aureus, Bacillus subtilis, E. Coli, Ps. Aerugiosa* and *Candida albicans* were used. Antibiotic benzylpenicillin sodium salt, gentamicin and cephalosporin antibiotic of the third generation — ceftriaxone were chosen with an antibacterial activity, and an antifungal activity — nystatin.

Results of the revealed growth inhibition on some media are shown in Table.

T a b l e

Antimicrobical and antifungal activities of samples.
Diameters of growth inhibition of test-strains. Solvent is 96 % ethanol

No.	Studied substances	*S. aureus*	*B. subtilis* 6633	*E. coli*	*Ps. aerugiosa* ATCC 9027	*C. alblcans*
1	(E)-1,3-bis(2- hydroxyphenyl)-prop-2-en-1-one (2)	20±1.0	18±1.0	10±1.0	10±1.0	11±1.0
2	(E)-1-(2-hydroxyphenyl)-3-(4-hydroxy-phenyl)-prop-2-en-1-one (4)	19±1.0	11±1.0	11±1.0	10±1.0	10±1.0
3	(E)-3-(ethoxy-4-hydroxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (5)	18±1.0	14±1.0	12±1.0	11±1.0	11±1.0
4	2,2-(4,5-dihydro-1H-pyrazole-3,5-diil)phenol (8)	14±1.0	13±1.0	13±1.0	11±1.0	12±1.0
5	4-[5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-3-il]benzol-1,3-diol (9)	14±1.0	11±1.0	10±1.0	10±1.0	15±1.0
6	2-(2-hydroxyphenyl)flavone-4-one (12)	18±1.0	11±1.0	10±1.0	10±1.0	11±1.0
7	2-(4-hydroxyphenyl)flavone-4-one (14)	14±1.0	13± 1.0	13±1.0	11±1.0	12±1.0
8	96 % Ethanol	9±1.0	9±1.0	9±1.0	9±1.0	9±1.0
9	Benzylpenicillin sodium salt	15±1.0	–	16±1.0	12±1.0	–
10	Gentamicin	22±1.0	30±1.0	31±1.0	30±1.0	–
11	Ceftriaxone	30±1.0	30±1.0	29±1.0	22±1.0	–
12	Nystatin	–	–	–	–	25±1.0

These cultures were seeded with a lawn method on the following media, namely egg yolk high salt agar, Endo agar, nutrient agar and Sabouraud's medium. Then Petri dishes were incubated for a day at 37 ºC, for fungi at 28 ºC.

Thus, as a result of this research there was established that practically all studied substances showed a weak antibacterial activity. Exception is *S. aureus* culture for compounds of (E)-1.3-bis (2-hydroxyphenyl)-prop-2-en-1-one (**2**), (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)-prop-2-en-1-one (**4**), (E)-3-(ethoxy-4-hydroxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**5**) and 2-(2-hydroxyphenyl)flavone (**12**) which possess the moderate actions.

Experimental

^{1}H and ^{13}C NMR spectra of compounds 1–15 were recorded on JNN-ECA Jeol 400 spectrometer (frequency 399.78 and 100.53 MHz, respectively) in DMSO-d_6 a solvent. The chemical shifts were measured concerning signals of residual protons or carbon atoms of DMSO-d_6. The control of the reaction and purity of

the compounds obtained was performed by Thin Layer Chromatography method on Silufol UV-254 plates in isopropyl alcohol-benzene-ammonia system (10:5:2). Plates were processed with iodine vapour.

General procedure of the receiving of chalcones (1–6)

The substituted acetophenone (0.013 mol) solution and aromatic aldehyde (0.013 mol) in ethanol (20 ml) were dropped to 20 ml of sodium hydroxide solution (40 %) at stirring and a room temperature. In process of aldehyde addition the reactionary mixture had yellow colour. The reactionary mixture was kept at room temperature for 62–95 h. Then the reactionary mixture was acidified with the diluted hydrochloric acid to neutral medium and kept for night in refrigerator (at temperature –15 ºC). The dropped out light brown powder was filtered, dried and recrystallized from benzene.

(E)-1-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (1). Product yield of 1 is 36 %, m.p. is 186–187 ºC. ^{1}H NMR spectrum, δ, ppm: 3.76 s (3H, H^{8}), 6.86 d (2H, $H^{15,17}$, ^{3}J 9.2 Hz), 6.95 d (2H, $H^{2,6}$, ^{3}J 8.5 Hz), 7.62 d (1H, H^{10}, ^{3}J 15.3 Hz), 7.74 d (1H, H^{9}, ^{3}J 17.1 Hz), 7.77 d (2H, $H^{3,5}$, ^{3}J 8.6 Hz), 8.03 d (2H, $H^{14,18}$, ^{3}J 8.5 Hz), 10.39 br. s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 55.83 (C^{8}), 114.87 ($C^{2,6}$), 115.88 ($C^{15,17}$), 120.08 (C^{9}), 128,04 (C^{4}), 129.84 (C^{13}), 131.05 ($C^{3,5}$), 131.57 ($C^{14,18}$), 143.21(C^{10}), 161.62 (C^{1}), 162.61 (C^{16}) and 187.57 (C^{11}).

(E)-1,3-bis(2-hydroxyphenyl)-prop-2-en-1-one (2). Product yield of 2 is 84 %, m.p. is 154–155 ºC. ^{1}H NMR spectrum, δ, ppm: 6.85 t (H, H^{14}, ^{3}J 8.7 Hz), 6.90–6.98 m (3H, $H^{4,6,10}$), 7.26 t (1H, H^{15}, ^{3}J 8.2 Hz), 7.51 t (1H, H^{5}, ^{3}J 7.8 Hz), 7.81 d (1H, H^{17}, ^{3}J 9.6 Hz), 7.89 d (1H, H^{16}, ^{3}J 15.6 Hz), 8.07–8.13 m (2H, $H^{3,10}$). ^{13}C NMR spectrum, δ, ppm: 116.75 (C^{14}), 118.04 (C^{10}), 119.87 (C^{6}), 121.03 (C^{4}), 121.11 (C^{16}), 121.45 (C^{2}), 121.83 (C^{12}), 129.55 (C^{17}), 131.08 (C^{3}), 132.80 (C^{15}), 136.64 (C^{5}), 140.95 (C^{11}), 158.10 (C^{13}), 194.44 (C^{8}).

(E)-1-(2,4-Dihydroxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (3). Product yield of 3 is 23.4 %, m.p. is 175–176 ºC. ^{1}H NMR spectrum, δ, ppm: 3.78 s (3H, H^{20}), 6.08 d (1H, H^{6}, ^{4}J 2.3 Hz), 6.26 dd (1H, H^{4}_{apom}, ^{3}J 2.1, 8.9 Hz), 6.97 d (2H, $H^{15,17}$, ^{3}J 8.7 Hz), 7.69–7.77 m (2H, $H^{11,12}$), 7.79 d (2H, $H^{14,18}$, ^{3}J 8.7 Hz), 8.01 d (1H, H^{3}, ^{3}J 9.2 Hz). ^{13}C NMR spectrum, δ, ppm: 55.88 (C^{20}), 110.54 (C^{6}), 111.51 (C^{4}), 114.91 (C^{2}), 114.92 ($C^{15,17}$), 119.52 (C^{11}), 128.06 (C^{13}), 131.21 ($C^{14,18}$), 133.08 (C^{12}), 142.94 (C^{3}), 161.73 (C^{16}), 166.92 (C^{1}), 167.30 (C^{5}), 190.52 (C^{8}).

(*E)-1-(2- hydroxyphenyl)-3-(4-hydroxyphenyl)-prop-2-en-1-one* (4). Product yield of 4 is 37 %, m.p. is 155–156 ºC. ^{1}H NMR spectrum, δ, ppm: 6.82 d (2H, $H^{13,17}$, ^{3}J 8.7 Hz), 6.94 m (1H, H^{4}), 6.96 d (1H, H^{11}, ^{3}J 11.9 Hz), 7.49 m (1H, H^{3}), 7.69–7.75 m (2H, $H^{5,6}$), 7.72 d (2H, $H^{14,16}$, ^{3}J 8.7 Hz), 8.5 d (1H, H^{10}, ^{3}J 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 116.37 (C^{13}), 116.67 (C^{17}), 118.39 (C^{11}), 119.60 (C^{4}), 121.20 (C^{2}), 126.17 (C^{12}), 131.05 (C^{10}), 131.87 (C^{14}), 131.94 (C^{16}), 136.53 (C^{3}), 146.10 ($C^{5,6}$), 161.12 (C^{15}), 162.51 (C^{1}), 194.13 (C^{8}).

(E)-3-(ethoxy-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-prop-2-en-1-one (5). Product yield of 5 is 72 %, m.p. is 151–152 ºC. ^{1}H NMR spectrum, δ, ppm: 1.33 t (3H, H^{9}, ^{3}J 6.9 Hz), 4.11 k (2H, H^{8}, ^{3}J 6.9 Hz), 6.83 d (1H, H^{17}, ^{3}J 8.2 Hz), 6.93 t (1H, H^{3}, ^{3}J 8.2 Hz), 6.97 d (1H, H^{12}, ^{3}J 7.8 Hz), 7.27 dd (1H, H^{18}, ^{3}J 8.2, 1.8 Hz), 7.50 m (2H, $H^{4,6}$), 7.75 m (2H, $H^{19,20}$), 8.19 d (1H, H^{11}, ^{3}J 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 15.26 (C^{9}), 64.82 (C^{8}), 114.11 (C^{4}), 116.39 (C^{17}), 118.06 (C^{11}), 118.45 (C^{3}), 119.36 (C^{20}), 121.14 (C^{15}), 125.35 (C^{18}), 126.16 (C^{5}), 131.28 (C^{12}), 136.67 (C^{6}), 146.59 (C^{19}), 147.77 (C^{1}), 153.13 (C^{2}), 162.59 (C^{16}), 194.17 (C^{13}).

(E)-1-(4-bromphenyl)-3-(5-brom-2-hydroxyphenyl)-prop-2-en-1-one (6). Product yield of 6 is 35 %, m.p. is 184–185 ºC. ^{1}H NMR spectrum, δ, ppm: 6.84 d (1H, H^{3}, ^{3}J 9.2 Hz), 7.37 dd (1H, H^{2}, ^{3}J 8.7, 2.3 Hz), 7.73 d (2H, $H^{15,17}$, ^{3}J 7.4 Hz), 7.86–7.96 m (2H, $H^{6,10}$), 8.05 d (2H, $H^{14,18}$, ^{3}J 8.3 Hz), 8.11 d (1H, H^{9}, ^{3}J 2.3 Hz). ^{13}C NMR spectrum, δ, ppm: 111.40 (C^{1}), 118.85 (C^{3}), 121.99 (C^{10}), 124.05 (C^{5}), 127.85 (C^{16}), 130.85 (C^{6}), 132.35 ($C^{15,17}$), 134.97 (C^{2}), 137.07 (C^{13}), 138.47 (C^{9}), 178.78 (C^{11}).

General procedure of the receiving of substituted pyrazolines (7–11)

0.02 mol of hydrazine hydrate was added to substituted chalcone (0.002 mol) in 10 ml of ethanol. Mixture was heated at temperature 70–80 ºC for 4 h, then cooled and diluted in 50 ml of water. A dropped out residue was filtered, washed with water and recrystallized from ethanol.

4-[5-[5-(4-Methoxyphenyl)-4,5-dihydro-1H-pyrazole-3-yl]]phenol (7). Product yield of **7** is 53 %, m.p. is 119–120 ºC. ^{1}H NMR spectrum, δ, ppm: 2.68 dd (1H, H^{4ax}, ^{2}J 16.3 Hz, ^{3}J 11.0 Hz), 3.27 dd (1H, H^{4eq}, ^{2}J 16.5 Hz, ^{3}J 10.5 Hz), 3.67 s (1H, H^{20}), 4.68 t (1H, H^{5}, ^{3}J 10.1 Hz), 6.72 d (2H, $H^{8,10}$, ^{3}J 8.7 Hz), 6.84 d (2H, $H^{14,16}$, ^{3}J 8.7 Hz), 7.21 d (2H, $H^{13,17}$, ^{3}J 8.7 Hz), 7.40 d (2H, $H^{7,11}$, ^{3}J 8.2 Hz), 9.67 br. s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 41.42 (C^{4}), 55.55 (C^{5}), 63.51 (C^{20}), 114.22 ($C^{14,16}$), 115.84 ($C^{8,10}$), 124.92 (C^{6}), 127.52 ($C^{13,17}$), 128.28 ($C^{7,11}$), 135.51 (C^{12}), 149.71 (C^{3}), 158.16 (C^{15}), 158.86 (C^{9}).

2,2'-(4,5-dihydro-1H-pyrazole-3,5-diil)phenol (8). Product yield of 8 is 72 %, m.p. is 124–125 ºC. ^{1}H NMR spectrum, δ, ppm: 2.88 dd (1H, CH^{4ax}, ^{2}J 16.5 Hz, ^{3}J 10.1 Hz), 3.53 dd (1H, CH^{4eq}, ^{2}J 16.7 Hz, ^{3}J 10.7 Hz), 5.00 t (1H, CH^{5}, ^{3}J 10.5 Hz), 6.72–6.87 m (4H, $CH^{8,10,14,16}_{apom}$), 7.03–7.07 m (1H, CH^{11}_{apom}), 7.15–

7.18 m (1H, CH^{17}_{apom}), 7.25 t (2H, $CH^{9,15}_{apom}$, ^{3}J 7.8 Hz), 7.50 br. s (1H, NH). NMR ^{13}C spectrum, δ, ppm: 40.01 (C^4), 57.67 (C^5), 115.63 (C^8), 115.91 (C^{14}), 116.41 (C^{10}), 117.45 (C^{16}), 119.50 ($C^{6,12}$), 127.38 (C^{17}), 128.06 (C^{15}), 128.54 (C^9), 130.00 (C^{11}), 153.46 (C^3), 155.33 (C^{13}), 157.28 (C^7).

4-[5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-3-il]benzol-1,3-diol (9). Product yield of 9 is 37 %, m.p. is 149–150ºC. ^{1}H NMR spectrum, δ, ppm: 2.84 dd (1H, H^{4ax}, ^{2}J 11.0 Hz, ^{3}J 11.0 Hz), 3.43 dd (1H, H^{4eq}, ^{2}J 5.3 Hz, ^{3}J 10.5 Hz), 3.70 s (3H, H^{21}),4.68 t (1H, H^5, ^{3}J 10.5 Hz), 6.27 m (2H, $H^{8,10}$), 6.87 d (2H, $H^{14,16}$, ^{3}J 8.7 Hz), 7.05 d (1H, H^{11}, ^{3}J 8.7 Hz), 7.27 d (2H, $H^{13,17}$, ^{3}J 8.7 Hz), 11.22 br. s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 41.59 (C^4), 55.62 (CH_3), 61.86 (C^5), 102.92 (C^8), 107.50 (C^{10}), 109.44 (C^6), 114.35 ($C^{14,16}$), 128.39 ($C^{13,17}$), 129.40 (C^{11}), 134.76 (C^{12}), 153.87 (C^3), 159.09 (C^9), 159.74 (C^{15}), 162.10 (C^7).

2-[5-[5-(4-Hydroxyphenyl)-4,5-dihydro-1H-pyrazole-5-yl]phenol (10). Product yield of 10 is 89 %, m.p. is 110–111 ºC. ^{1}H NMR spectrum, δ, ppm: 2.89 dd (1H, H^{4ax}, ^{2}J 15.8 Hz, ^{3}J 10.8 Hz), 3.47 dd (1H, H^{4eq}, ^{2}J 16.5 Hz, ^{3}J 11.0 Hz), 4.69 t (1H, H^5, ^{3}J 9.8 Hz), 6.70 d (2H, $H^{14,16}$, ^{3}J 7.3 Hz), 6.81–6.87 m (2H, $H^{8,10}$), 7.13–7.19 m (3H, $H^{9,13,17}$), 7.24 d (2H, H^{11}, ^{3}J 7.3 Hz), 7.68 br. s (1H, NH), 9.35 s (1H, OH^{19}), 11.16 s (1H, OH^{18}). ^{13}C NMR spectrum, δ, ppm: 41.24 (C^4), 62.36 (C^5), 115.68 ($C^{14,16}$), 116.23 (C^8), 117.35 (C^6), 119.65 (C^{10}), 128.25 (C^{11}), 128.37 ($C^{13,17}$), 130.17 (C^9), 132.79 (C^{12}), 153.06 (C^3), 157.22 (C^{15}), 157.26 (C^7).

2-Etoxy-4-[3-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-5-yl]phenol (11). Product yield of 11 is 93 %, m.p. is 89–90 ºC. ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, H^{21}, ^{3}J 7.3 Hz), 2.92 dd (1H, H^{4ax}, ^{2}J 16.5 Hz, ^{3}J 11.0 Hz), 3.49 dd (1H, H^{4eq}, ^{2}J 16.8 Hz, ^{3}J 11.0 Hz), 3.96 q (2H, H^{20}, ^{3}J 6.7 Hz), 4.69 t (1H, H^5, ^{3}J 11.0 Hz), 6.69–6.74 m (2H, $H^{10,14}$), 6.82–6.92 m (3H, $H^{8,13,17}$), 7.16 d (1H, H^{11}, ^{3}J 7.3 Hz), 7.25 t (1H, H^9, ^{3}J 7.3 Hz), 7.71 s (1H, NH), 8.87 br. s (1H, OH^{19}), 11.16 s (1H, OH^{18}). ^{13}C NMR spectrum, δ, ppm: 15.32 (C^{21}), 41.31 (C^4), 62.65 (C^5), 64.37 (C^{20}), 112.75 (C^{17}), 115.88 (C^{10}), 116.23 (C^8), 117.37 (C^6), 119.65 (C^{13}), 119.69 (C^{14}), 128.26 (C^9), 130.18 (C^{11}), 133.29 (C^{12}), 146.68 (C^{15}), 147.17 (C^{16}), 153.16 (C^3), 157.26 (C^7).

General procedure of the receiving of flavanones (12–15)

The reactionary mixture from 0.001 mol of substituted chalcone and catalytic amount of triethylamine in 15 ml of ethanol (95 %) was heated with backflow condenser for 8 h. The dropped out residue was filtered. It was dried at room temperature.

2-(2-hydroxyphenyl)flavone-4-one (12). Product yield of 12 is 94 %, m.p. is 147–148 ºC. ^{1}H NMR spectrum, δ, ppm: 2.76 dd (1H, H^{3ax}, ^{2}J 16.7 Hz, ^{3}J 2.7 Hz), 3.14 dd (1H, H^{3eq}, ^{2}J 17.0, Hz, ^{3}J 13.3 Hz), 5.75 dd (1H, H^2, ^{3}J 13.3, 2.8 Hz), 6.77–6.83 m (3H, $H^{13,14,15}$), 7.05 d (1H, H^{16}, ^{3}J 7.8 Hz), 6.86 d (1H, H^7, ^{3}J 8.2 Hz), 7.13 t (1H, H^{10}, ^{3}J 8.2 Hz), 7.49 t (1H, H^8, ^{3}J 7.8 Hz), 7.54 t (1H, H^9, ^{3}J 6.9 Hz), 8.09 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 43.02 (C^3), 74.85 (C^2), 116.31(C^{13}), 118.27 (C^5), 118.71 (C^7), 119.78 (C^{15}), 121.64 (C^8), 122.07 (C^9), 125.58 (C^{16}), 126.89 (C^{10}), 127.34 (C^{14}), 130.04 (C^{11}), 136.79 (C^{12}), 154.84 (C^6), 162.03 (C^4).

7-Hydroxy-2-(4-methoxyphenyl)flavone-4-on (13). Product yield of 13 is 76 %, m.p. is 146–147 ºC. ^{1}H NMR spectrum, δ, ppm: 2.59 dd (1H, H^{3ax}, ^{2}J 16.9 Hz, ^{3}J 2.8 Hz), 3.08 dd (1H, H^{3eq}, ^{2}J 16.7 Hz, ^{3}J 16.1 Hz), 3.71 s (3H, H^{20}), 5.45 dd (1H, H^2, ^{3}J 12.8, 2.3 Hz), 6.29 s (1H, H^7), 6.46 d (1H, H^9, ^{3}J 8.0 Hz), 6.97 d (2H, $H^{13,15}$, ^{3}J 8.2 Hz), 7.39 d (2H, $H^{12,16}$, ^{3}J 8.7 Hz), 8.14 d (1H, H^{10}, ^{3}J 8.7 Hz), 10.62 br. s. (1H, OH^{18}). ^{13}C NMR spectrum, δ, ppm: 43.67 (C^3), 55.65 (C^{20}), 79.25 (C^2), 103.09 (C^7), 111.08 (C^9), 114.33 ($C^{13,15}$), 114.94 (C^5), 128.74 ($C^{12,16}$), 131.54 (C^{10}), 133.51 (C^{11}), 159.85 (C^{14}), 165.16 (C^6), 166.34 (C^8), 190.59 (C^4).

2-(4-hydroxyphenyl)flavone-4-one (14). Product yield of 14 is 95 %, m.p. is 184–185 ºC. ^{1}H NMR spectrum, δ, ppm: 2.73 dd (1H, H^{3ax}, ^{2}J 16.9 Hz, ^{3}J 3.2 Hz), 3.18 dd (1H, H^{3eq}, ^{2}J 16.5, Hz, ^{3}J 12.8 Hz), 5.48 dd (1H, H^2, ^{3}J 12.8, 2.8 Hz), 6.77 d (2H, $H^{13,15}$, ^{3}J 8.2 Hz), 7.30 d (2H, $H^{12,16}$, ^{3}J 8.3 Hz), 7.00–7.05 m (2H, $H^{7,9}$), 7.52 t (1H, H^8, ^{3}J 8.2 Hz, 7.75 d (1H, H^{10}, ^{3}J 7.9 Hz), 9.48 br. s (1H, OH^{18}). ^{13}C NMR spectrum, δ, ppm: 43.94 (C^3), 79.40 (C^2), 115.82 (C^{13}), 115.92 (C^{15}), 118.76 ($C^{7,9}$), 121.19(C^5), 128.54 (C^{12}), 128.91 (C^{16}), 129.69 (C^{11}), 136.80 (C^8), 158.19 (C^{14}), 161.77 (C^6), 192.40 (C^4).

2-(3-etoxy-4-hydroxyphenyl)flavone-4-one (15). Product yield of 15 is 96 %, m.p. is 127–128 ºC. ^{1}H NMR spectrum, δ, ppm: 1.29 t (3H, H^{20}, ^{3}J 6.9 Hz), 2.71 dd (1H, H^{3ax}, ^{2}J 17.0 Hz, ^{3}J 2.7 Hz), 3.26 dd (1H, H^{3eq}, ^{2}J 17.0 Hz, ^{3}J 13.3 Hz), 4.00 k (2H, H^{19}, ^{3}J 6.9 Hz), 5.47 dd (1H, CH_2, ^{3}J 12.8, 2.8 Hz), 6.78 d (1H, H^{16}, ^{3}J 8.2 Hz), 6.89 d (1H, H^{12}, ^{3}J 8.2 Hz), 7.02–7.06 m (3H, $H^{7,10,15}$), 7.53 t (1H, H^8, ^{3}J 8,2 Hz), 7.76 t (1H, H^9, ^{3}J 7.8 Hz), 9.00 s (1H, OH). NMR spectrum ^{13}C, δ, ppm: 15.29 (C^{20}), 44.03 (C^3), 64.55 (C^{19}), 79.57 (C^2), 113.10 (C^{12}), 115.86 (C^{15}), 118.57 (C^7), 120.20 (C^{16}), 121.15 (C^5), 121.81 (H^9), 126.81 (C^{10}), 130.18 (C^{11}), 136.71 ($C^8{}_a$), 147.20 (C^{14}), 147.77 (C^{13}), 161.76 (C^6), 192.47 (C^4).

The study was performed with support of the Ministry of Education and Science of the Republic of Kazakhstan (project number AP05133157).

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Ауыстырылған халкондардың және олардың туындыларының синтезі, құрылымы және микробқа қарсы белсенділігі

Мақалада гидроксилді орынбасылған ацетофенондармен ароматты орынбасылған альдегидтердің әрекеттесу реакцияларын, альдольді конденсацияда байқалатын сілтілі сулы-спиртті ерітіндінің (Кляйзен-Шмидт конденсациясы) қатысуымен зерттелді. Бұл реакцияның жүру ұзақтығы көп және аяқталу уақыты 62–85 сағ аралығын құрайды. Соңғы өнімнің құрылысында α,β-жағдайдағы карбонильді топтың қос байланысы бар. Алынған халкондардың функционализациялануы олардың гидразингидратпен әрекеттесуі жолы арқылы жүзеге асырылды. Этанолда халкондар гидразингидратпен қайнатылған кезде аралық гидразон, молекулаішілік циклоконденсацияға ұшырап, пиразол туындылары түзілді. Синтезделген қосылыстардың құрылысы ^{1}H-, ^{13}C-ЯМР-спектроскопия және екі шекті (^{1}H-^{1}H) COSY және (^{1}H-^{13}C) HMQC-спектрлері бойынша дәлелденді. Бірөлшемді ЯМР ^{1}H және ^{13}C спектрлерінде сигналдардың химиялық ығысуының, еселігінің және интегралдық қарқындылығының мәндері анықталды. Зерттелген қосылыстардың құрылымын дәлелдейтін гомо- және гетероядролық өзара әрекеттесулер (^{1}H-^{1}H) COSY және (^{1}H-^{13}C) HMQC спектрлері бойынша анықталды. Синтезделген халкондардың, пиразолиндер мен флавонондардың микробқа қарсы белсенділіктерінің мәліметтері келтірілген. Барлық зерттелген қосылыстар бактерияға қарсы әлсіз белсенділікті көрсетті. Қалыпты айқын әсерге ие (E)-1,3-бис(2-гидроксифенил)-проп-2-ен-1-он, (E)-1-(2-гидроксифенил)-3-(4-гидрокси-фенил)-проп-2-ен-1-он,

(Е)-3-(этокси-4-гидроксифенил)-1-(2-гидроксифенил)проп-2-ен-1-он, 2-(2-гидроксифенил)флавон қосылыстары үшін *S. aureus* ашытқы зеңдерінің дақылы.

Кілт сөздер: орынбасқан ароматикалық альдегид, халкон, пиразолин, флавонон, цитокин, NF-κB транскрипциондық факторы.

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Синтез, структура и антимикробная активность замещенных халконов и их производных

В статье приведены реакции взаимодействия гидроксилзамещенных ацетофенонов с замещенными ароматическими альдегидами в присутствии водно-спиртового раствора щелочи (конденсация Кляйзена-Шмидта), которая представляет собой альдольную конденсацию. Эта реакция имеет большую продолжительность и заканчивается в течение 62–85 ч. Конечный продукт содержит двойные связи в α,β-положении к карбонильной группе. Дальнейшую функционализацию полученных халконов осуществляли путем их взаимодействия с гидразингидратом. Было обнаружено, что кипячение халконов с гидразингидратом в этаноле приводит к внутримолекулярной циклоконденсации промежуточного гидразона с образованием производных пиразола. Структуры синтезированных соединений изучали с помощью ^{1}H и ^{13}C-ЯМР-спектроскопии и данных по двумерным (^{1}H-^{1}H) COSY и (^{1}H-^{13}C) HMQC-спектрам. Определены значения химических сдвигов, кратности и интегральной интенсивности сигналов в одномерных спектрах ЯМР ^{1}H и ^{13}C. Гомо- и гетероядерные взаимодействия, подтверждающие структуру изученных соединений, определяли по спектрам (^{1}H-^{1}H) COSY и (^{1}H-^{13}C) HMQC. Приведены данные по антимикробной активности синтезированных халконов, пиразолинов и флавононов. Установлено, что практически все исследованные вещества показывают слабую антибактериальную активность. Исключение составляет культура дрожжевых грибков *S. aureus* для соединений (Е)-1,3-бис(2-гидроксифенил)-проп-2-ен-1-он, (Е)-1-(2-гидроксифенил)-3-(4-гидрокси-фенил)-проп-2-ен-1-он, (Е)-3-(этокси-4-гидроксифенил)-1-(2-гидроксифенил)проп-2-ен-1-он, 2-(2-гидроксифенил)флавон, которые обладают умеренно выраженным действием.

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

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