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USE OF QUANTUM-CHEMICAL PARAMETERS FOR FORECASTING ANTIRADICAL (HO·) ACTIVITY OF RELATED STRUCTURES CONTAINING A CINNAMIC MOLD FRAGMENT.
III. CHALCONES, FLAVANONES AND FLAVONES WITH PHLOROGLUCINIC TYPE OF RING "A"

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42 derivatives of chalcone, flavanone and flavone having a phloroglucinic type of ring "A" and containing the same electron-donating substituents on ring "B", have been studied. Flavonoids with the phloroglucinic type of ring "A" are the most common in nature, which is due to the peculiarities of biogenetic formation with the participation of malonyl and acetyl fragments.

The aim. To determine the effect of the hydroxy group in position 6' of chalcones and in position 5 of flavanones and flavones on bond numbers (Nµ), free valence indices (Fµ), Mulliken charges (a.e), electron density, unsaturation indices (IUA) of the carbon atoms C-1 → C-6 → C-7 → C-8.

Materials and methods. The calculations of the listed above parameters with the use of the semi-empirical method PM7 (WinMopac 2016 program) have been carried out on a workstation with an Intel Xeon E5-1620 3.5 GHz processor, 20 GB of RAM.

Results. The quantum-chemical characteristics of the considered derivatives having a phloroglucinic type of the "A" ring, indicate that the OH group in position 6' of chalcones (in the corresponding flavanones and flavones in position 5) has different effects: a slight increase occurs in chalcones negative charge (a.e.) and electron density, the bond numbers take different values, which depends on the position and number of substituents on the ring "B". In flavanones, Nµ practically remains at the same level of 3.822–3.829. For flavones, the binding numbers Nµ for C-8 are in the range of 3.700–3.706, and the Mulliken charges are in the range from –0.4120 to –0.4356. For position-substituted C-3 (6anone and 7anone), the charges are –0.4436 and –0.4479, respectively. The charge on C-7 of chalcones is negative for compounds 4x, 5x, 10x and 13x from –0.0204 to –0.0470. The remaining derivatives of the chalcone, as well as the corresponding flavanones and flavones, are characterized by a positive value of a.e. on C-7. Based on the bond numbers (Nµ), free valency indices (Fµ) have been found for the carbon atoms of the cinnamoyl fragment C-1 → C-6 → C-7 → C-8. When comparing the obtained data, it was found out that for chalcones on C-1 → C-8 atoms, the values of the free valence indices are in the range of 0.900–0.980 for compounds 12x, 13x, where Fµ>1. For flavanones on C-1, C-3, and C-5 atoms (compounds 12anone and 13anone), the free valence indices are in the range of 0.984-1.024, and for the remaining atoms the value of Fµ is approximately the same as that of chalcones. On the C-8 atoms of all the derivatives, as well as on C-1, C-3 and C-5 (compounds 12one, 13one), Fµ≥1.0. It can be assumed that at values of Fµ=0.850–0.955 for all the analyzed compounds, coupling reactions on the double bond are possible, and if Fµ≥1, the coupling will take place according to the free radical mechanism. The data obtained indicate that the OH group in position 6' for the chalcone and 5 for the flavanones, does not significantly effect the Mulliken charge (a.e) and the electron density on C-8 atoms.

Conclusion. It has been established that the OH group in position 6' of the "A" ring of chalcones (in position 5 of the "A" ring in flavones and flavanones) has a conflicting effect on the bond numbers: when passing from chalcone to flavanone, Nµ increases, and then, in flavone, sharply decreases. For C-8 of all flavone derivatives, Fµ≥1. The following conclusion has been confirmed: at the initial stage of the reaction the electrophilic hydroxyl radical is attached at the C-8 position of the cinnamoyl fragment

Keywords: 2',4',6'-threehydroxychalcones, 5,7-dihydroxyflavanones, 5,7-dihydroxyflavones, bond numbers, free valence indices

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ИСПОЛЬЗОВАНИЕ КВАНТОВО-ХИМИЧЕСКИХ ПАРАМЕТРОВ ДЛЯ ПРОГНОЗИРОВАНИЯ АНТИРАДИКАЛЬНОЙ (НО·) АКТИВНОСТИ РОДСТВЕННЫХ СТРУКТУР, СОДЕРЖАЩИХ ЦИННАМОИЛЬНЫЙ ФРАГМЕНТ.

III. ХАЛКОНЫ, ФЛАВАНОНЫ И ФЛАВОНЫ С ФЛОРОГЛЮЦИНОВЫМ ТИПОМ КОЛЬЦА «А»

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Изучено 42 производных халкона, флаванона и флавона, имеющих флороглюциновый тип кольца «А» и содержащих одинаковые электронодонорные заместители в кольце «В». Флавоноиды с флороглюциновым типом кольца «А» наиболее распространены в природе, что обусловлено особенностями биогенетического формирования при участии малонильных и ацетильных фрагментов.

Цель. Выявление влияния гидроксигруппы в положении 6′ у халконов и в положении 5 у флаванонов и флавонов на связевые числа (Nμ); индексы свободной валентности (Fμ); Малликеновские заряды (a.e); электронную плотность; индексы ненасыщенности (IUA) атомов углерода C-1→C-6→C-7→C-8.

Материалы и методы. Перечисленные выше квантово-химические параметры анализируемых соединений рассчитаны полуэмпирическим методом PM7 (программа WinMopac 2016) на рабочей станции с процессором Intel Xeon E5-1620 3,5 ГГц, 20 Гб оперативной памяти.

Результаты. Квантово-химические характеристики рассматриваемых производных, имеющих флороглюциновый тип кольца «А», свидетельствуют о том, что ОН-группа в положении 6′ у халконов, (у соответствующих флаванонов и флавонов в положении 5) влияет по-разному: у халконов имеет место незначительное повышение отрицательного заряда (a.e) и электронной плотности, связевые числа принимают разные значения, что зависит от положения и числа заместителей в кольце «В». У флаванонов Nμ практически остается на одном уровне 3,822–3,829. У флавонов значения связевых чисел Nμ у C-8 находятся в интервале 3,700–3,706, а Малликеновские заряды находятся в пределах от –0,4120 до –0,4356. У замещенных по положению С-3 (6-флаванон и 7-флаванон) заряд равен –0,4436 и –0,4479 соответственно. У халконов заряд на С-7 имеет отрицательное значение у соединений 4х, 5х, 10х и 13х от –0,0204 до –0,0470. Остальные производные халкона, а также соответствующие флаваноны и флавоны, характеризуются положительным значением a.e на С-7. Исходя из связевых чисел (Nμ), найдены индексы свободной валентности (Fμ) для атомов углерода циннамоильного фрагмента C-1→C-6→C-7→C-8. При сопоставлении полученных данных установлено, что у халконов на атомах С-1→С-8 значения индексов свободной валентности находятся в пределах 0,900–0,980 у соединений 12х, 13х, где Fμ>1. У флаванонов на атомах С-1, С-3 и С-5 (соединения 12анон и 13анон) индексы свободной валентности находятся в интервале 0,984–1,024, а у остальных атомов величина Fμ примерно такая же, как у халконов. На атомах С-8 всех производных, а также С-1, С-3 и С-5 (соединения 12он, 13он) Fμ≥1,0. Можно предположить, что при значениях Fμ=0,850–0,955 для всех анализируемых соединений возможны реакции присоединения по двойной связи, а если Fμ≥1, то присоединение будет проходить по свободнорадикальному механизму. Полученные данные свидетельствуют о том, что ОН-группа в положении 6′ у халкона и 5 у флаванонов – не оказывает существенного влияния на Малликеновский заряд (a.e) и электронную плотность на атомах С-8.

Заключение. На основании полученных данных установлено, что ОН-группа в положении 6′ кольца «А» халконов (в положении 5 у флавонов и флаванонов) разнонаправлено влияет на величину связевых чисел: при переходе от халкона к флаванону Nμ возрастает, а затем у флавона резко уменьшается. Для атомов С-8 всех производных флавона Fμ≥1. Это вновь доказывает высказанный ранее нами вывод, что на начальном этапе электрофильный гидроксильный радикал присоединяется по положению С-8 циннамоильного фрагмента.

Ключевые слова: 2,′4′,6′-тригидроксихалконы; 5,7-дигидроксифлаваноны; 5,7-дигидроксифлавоны; связевые числа; индексы свободной валентности

INTRODUCTION

In nature, flavonoids with the phloroglucinic type of ring “A” [1–4] are the most common.

With reference to the previous reports [5, 6], this paper presents an interpretation of the quantum-chemical characteristics of chalcone, flavanone and flavone derivatives, characterized by a phloroglucinic type of ring (42 compounds in total) and having electron-donating substituents on ring “B”.

THE AIM of the article is to determine the effect of the hydroxy group in position 6′ of chalcone derivatives, which upon heterocyclization react to form the corresponding flavanones and flavones, on the quantum-chemical parameters; as well as the calculation of the free valence indices (Fμ) of the carbon atoms of the main conjugation chain to explain the reactivity of the compounds under study relative to the hydroxyl radical OH.

MATERIALS AND METHODS

The calculations of the listed above parameters with the use of the semi-empirical method PM7 (WinMopac 2016 program), have been carried out on a workstation with an Intel Xeon E5-1620 3.5 GHz processor, 20 GB of RAM.

RESULTS AND DISCUSSION

This report presents the data on the analysis of the quantum chemical characteristics of the structures presented in Table 1.

Bond numbers (Nμ), free valence indices (Fμ)

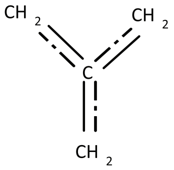
The reactivity of organic molecules is conveniently explained taking into account the free valence indices of the corresponding regions. There is a relationship between this parameter and the bond number [7]:

$$F\mu = N_{max} - N\mu$$

It is appropriate here to describe the physical meaning of the bond number in more details, because it is actually the sum of the orders of all the bonds adjacent to this atom [7].

The value of Nμ reflects the degree of saturation of a particular atom: the larger Nμ, the more saturated a particular atom is and, conversely, the lower the value of Nμ, the more pronounced is the tendency of a given atom to form new bonds.

The theoretical maximum of the sum of the bond orders should be 4.732, which is considered a constant value. It corresponds to the sum of the bond orders of a carbon atom bound by three σ-bonds and three π-bonds with neighboring atoms in the threemethylmethane biradical [8, 9].



It should be notified that by the value of Fμ one can judge the possibility of an addition reaction involving the compounds containing π-bonds: the higher Fμ, the more pronounced the activity of the addition of neutral particles. For values of Fμ>1, a radical mechanism will prevail in these reactions.

Tables 2–4 shows the numerical values of the free valence indices of carbon atoms of the main conjugation chain of the analyzed groups of compounds.

Derivatives of 2',4', 6'-threehydroxychalcones

In the absence of substituents on the B ring (compound 1x), the C-8 atom is characterized by the smallest value of bond number 3.799 (Fμ = 0.953); therefore, the attachment of the hydroxyl radical is most likely due to this position.

The bond numbers for C-1 and C-5 (3.813) with a free valence index of 0.919 for both atoms, are slightly larger. For the rest of the atoms C-2, C-4, C-6 and C-7, the values of Nμ are in the range of 3.850, with a value of Fμ from 0.881 to 0.884.

The introduction of a hydroxy group into the C-1 position of the "B" ring (compound 2x) helps to reduce the bond number of this atom to 3.745 (Fμ = 0.987 at a.e. +0.3426) compared to the same position for the unsubstituted ring B, where Nμ = 3.813 (Fμ = 0.919 with a.e. = –0.1183). In the same compound, C-8 has the smallest bond number (Nμ = 3.732, Fμ = 1.000, a.e = –0.3721), and at the C-6 atom Nμ = 3.765 (Fμ = 0.967, a.e = –0.2414).

Relatively low values of the bond numbers and free valence indices are characterized by positions C-2 and C-5, where Nμ are equal to 3.788 (Fμ = 0.944) and 3.806 (Fμ = 0.926). Replacing the OH group in C-1 by OCH_3 retains the indicated patterns at the C-1, C-2, C-5, C-6, and C-8 atoms (Table 2).

There is OH group in the C-2 position of compound 4x, and this contributes to a decrease in the bond number at the C-1 atoms (Nμ = 3.752, Fμ = 0.980, a.e = -0.2504), C-3 (Nμ = 3.769, Fμ = 0.963, a.e = –0.3068). At C-8, the value of Nμ is significantly lower (Nμ = 3.822, Fμ = 0.910, a.e = –0.3225) than at C-1 and C-3.

The methoxy group in position C-2 (compound 5x) contributes to a decrease in the bond number by C-1 (Nμ = 3.746, Fμ = 0.986, a.e = –0.2567) and C-3 (Nμ = 3.767, Fμ = 0.965 , a.e = –0.2964). As for the C-8 atom, here Nμ = 3.823 (Fμ = 0.909, a.e = –0.3575).

The hydroxy group in position C-3 (compound 6x) contributes to a significant decrease in the bond number (Nμ = 3.768, Fμ = 0.964, a.e = -0.3475) compared to other carbon atoms in the compound 6x. Rather low bond numbers are recorded for C-2 (Nμ = 3.788, Fμ = 0.944, a.e = –0.2618) and C-4 (Nμ = 3.778, Fμ = 0.954, a.e = –0.3219). In the case of OCH_3 in position C-3 (compound 7x), practically the same features as in 6x, are retained.

Two hydroxy groups or two methoxy groups (compounds 8x and 11x) in positions C-2 and C-3 have a competitive effect on the propenone fragment C-7 → C-8 → C-9. According to the σ-Taft constants of the substituents for the C-3-OH group, σ = –0.370, for OCH_3 σ = –0.268; for C-2-OH groups, σ = +0.127, for OCH_3 σ = +0.115 [10]. This type of substitution contributes to a decrease in Nμ to 3.763 and 3.765 (C-2 and C-3 di-OH), 3.765 and 3.777 (C-2 and C-3 di-OCH_3) at C-4 and C-5 atoms, respectively, ring "B").

For compounds 9x and 10x, where 2-OH and 3-OCH_3 (2-OCH_3 and 3-OH) groups are presented, almost all Nμ and Fμ values are the same on all carbon atoms of the propenone fragment.

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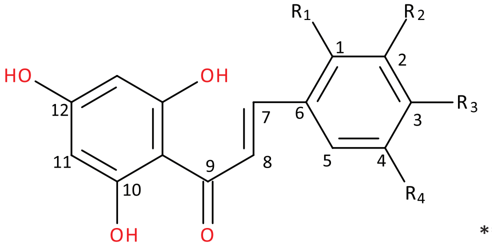
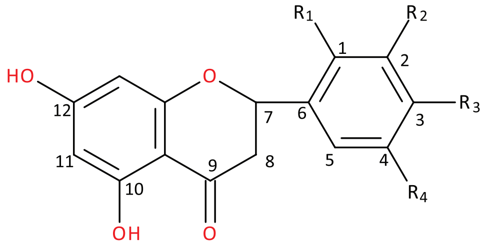
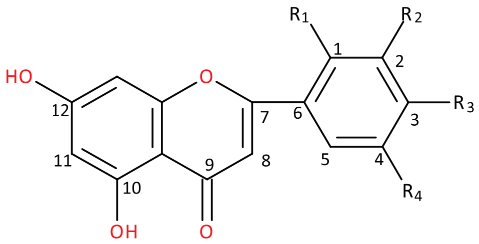
Table 1 – Chalcone, flavanone and flavone derivatives with a phloroglucinic type of ring A*

Com-pounds, Ser. No.				**								
	Chalcones				Flavanones				Flavones			
	X				anone				one			
	The nature of the substituents on the ring "B"											
	1	2	3	4	1	2	3	4	1	2	3	4
1	H	H	H	H	H	H	H	H	H	H	H	H
2	OH	H	H	H	OH	H	H	H	OH	H	H	H
3	OCH_3	H	H	H	OCH_3	H	H	H	OCH_3	H	H	H
4	H	OH	H	H	H	OH	H	H	H	OH	H	H
5	H	OCH_3	H	H	H	OCH_3	H	H	H	OCH_3	H	H
6	H	H	OH	H	H	H	OH	H	H	H	OH	H
7	H	H	OCH_3	H	H	H	OCH_3	H	H	H	OCH_3	H
8	H	OH	OH	H	H	OH	OH	H	H	OH	OH	H
9	H	OCH_3	OH	H	H	OCH_3	OH	H	H	OCH_3	OH	H
10	H	OH	OCH_3	H	H	OH	OCH_3	H	H	OH	OCH_3	H
11	H	OCH_3	OCH_3	H	H	OCH_3	OCH_3	H	H	OCH_3	OCH_3	H
12	H	OH	OH	OCH_3	H	OH	OH	OCH_3	H	OH	OH	OCH_3
13	H	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	OCH_3
14	H	$C(CH_3)_3$	OH	$C(CH_3)_3$	H	$C(CH_3)_3$	OH	$C(CH_3)_3$	H	$C(CH_3)_3$	OH	$C(CH_3)_3$

Note: * – Chalcone, flavanone and flavone derivatives under No. 14 are virtual and, in accordance with the forecast, will be synthesized later; ** – Numbering of carbon atoms corresponds to the numbers generated by the calculation programs

Table 2 – The values of the bond numbers (Nμ) and free valency indices (Fμ) on the C-1 → C-6 → C-7 → C-8 atoms of the main conjugation chain of the 2′,4′,6′-threehydroxychalcone derivatives. ***Fμ=N**$_{max}$***–Nμ**

Ser. No.	Carbons	C-1		C-2		C-3		C-4		C-5		C-6		C-7		C-8	
	R	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ
1	$R_1=R_2=R_3=R_4=H$	3.813	0.919	3.851	0.881	3.835	0.897	3.853	0.879	3.813	0.919	3.858	0.874	3.848	0.884	3.779	0.953
2	$R_1=OH$. $R_2=R_3=R_4=H$	3.745	0.987	3.788	0.944	3.829	0.903	3.842	0.890	3.806	0.926	3.765	0.967	3.829	0.903	3.732	1.000
3	$R_1=OCH_3$. $R_2=R_3=R_4=H$	3.766	0.966	3.780	0.952	3.838	0.894	3.837	0.895	3.820	0.912	3.790	0.942	3.861	0.871	3.828	0.904
4	$R_2=OH$. $R_1=R_3=R_4=H$	3.752	0.980	3.793	0.939	3.769	0.963	3.846	0.886	3.806	0.926	3.856	0.876	3.877	0.855	3.822	0.910
5	$R_2=OCH_3$. $R_1=R_3=R_4=H$	3.746	0.986	3.796	0.936	3.767	0.965	3.847	0.885	3.804	0.928	3.857	0.875	3.875	0.857	3.823	0.909
6	$R_3=OH$. $R_1=R_2=R_4=H$	3.813	0.919	3.788	0.944	3.771	0.961	3.778	0.954	3.809	0.923	3.853	0.879	3.842	0.890	3.768	0.964
7	$R_3=OCH_3$. $R_1=R_2=R_4=H$	3.815	0.917	3.782	0.950	3.772	0.960	3.775	0.957	3.809	0.923	3.829	0.903	3.839	0.893	3.765	0.967
8	$R_2=R_3=OH$. $R_1=R_4=H$	3.805	0.927	3.786	0.946	3.762	0.970	3.763	0.963	3.765	0.967	3.837	0.895	3.845	0.887	3.773	0.953
9	$R_2=OCH_3$. $R_3=OH$. $R_1=R_4=H$	3.808	0.924	3.779	0.953	3.758	0.974	3.761	0.971	3.762	0.970	3.835	0.897	3.842	0.890	3.771	0.961
10	$R_2=OH$. $R_3=OCH_3$. $R_1=R_4=H$	3.809	0.923	3.788	0.944	3.760	0.972	3.763	0.969	3.764	0.968	3.840	0.892	3.873	0.859	3.810	0.922
11	$R_2=R_3=OCH_3$. $R_1=R_4=H$	3.805	0.927	3.779	0.953	3.750	0.982	3.765	0.967	3.757	0.975	3.835	0.897	3.840	0.892	3.768	0.964
12	$R_2=R_3=R_4=OH$. $R_1=H$	3.798	0.994	3.776	0.956	3.708	1.024	3.770	0.962	3.736	0.996	3.850	0.882	3.852	0.880	3.784	0.948
13	$R_2=R_3=R_4=OCH_3$. $R_1=H$	3.729	1.003	3.776	0.956	3.692	1.040	3.768	0.964	3.721	1.011	3.854	0.878	3.874	0.858	3.820	0.912
14	$R_2=R_4=C(CH_3)_3$. $R_3=OH$. $R_4=H$	3.794	0.938	3.794	0.938	3.748	0.984	3.790	0.942	3.798	0.934	3.834	0.898	3.858	0.874	3.788	0.944

Note: * – Numbering of carbon atoms of the main conjugation chain is given in accordance with the numbers generated by the calculation programs

Table 3 – The values of the bond numbers (Nμ) and free valence indices (Fμ) on the C-1 → C-6 → C-7 → C-8 atoms of the main conjugation chain of 5,7-dihydroxyflavanone derivatives

No.	Carbon atoms	C-1		C-2		C-3		C-4		C-5		C-6		C-7		C-8	
	R	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ
1	R_1=R_2=R_3=R_4=H	3.829	0.903	3.849	0.883	3.844	0.888	3.85	0.882	3.828	0.904	3.840	0.892	3.838	0.894	3.827	0.905
2	R_1=OH, R_2=R_3=R_4=H	3.776	0.956	3.795	0.937	3.842	0.89	3.843	0.889	3.822	0.91	3.770	0.962	3.832	0.900	3.819	0.913
3	R_1=OCH$_{3,}$ R_2=R_3=R_4=H	3.780	0.952	3.801	0.931	3.842	0.89	3.842	0.89	3.828	0.94	3.792	0.940	3.839	0.893	3.817	0.915
4	R_2=OH, R_1=R_3=R_4=H	3.762	0.970	3.792	0.94	3.773	0.959	3.845	0.887	3.814	0.918	3.841	0.891	3.839	0.893	3.826	0.906
5	R_2=OCH$_{3,}$ R_1=R_3=R_4=H	3.757	0.975	3.795	0.937	3.77	0.962	3.846	0.886	3.813	0.919	3.842	0.890	3.837	0.895	3.827	0.905
6	R_3=OH, R_1=R_2=R_4=H	3.828	0.904	3.785	0.947	3.784	0.948	3.777	0.955	3.823	0.909	3.820	0.912	3.835	0.897	3.826	0.906
7	R_3=OCH$_{3,}$ R_1=R_2=R_4=H	3.830	0.902	3.779	0.953	3.785	0.947	3.774	0.958	3.824	0.908	3.817	0.915	3.835	0.897	3.828	0.904
8	R_2=R_3=OH, R_1=R_4=H	3.764	0.968	3.778	0.954	3.749	0.983	3.798	0.934	3.832	0.919	3.832	0.900	3.837	0.895	3.827	0.905
9	R_2=OCH$_{3,}$ R_3=OH, R_1=R_4=H	3.759	0.973	3.776	0.956	3.746	0.986	3.796	0.936	3.814	0.918	3.833	0.899	3.836	0.896	3.829	0.903
10	R_2=OH, R_3=OCH$_{3,}$ R_1=R_4=H	3.767	0.965	3.771	0.961	3.754	0.978	3.792	0.94	3.814	0.918	3.831	0.901	3.835	0.897	3.826	0.906
11	R_2=R_3=OCH$_{3,}$ R_1=R_4=H	3.782	0.950	3.767	0.965	3.76	0.972	3.779	0.953	3.82	0.912	3.824	0.908	3.835	0.897	3.829	0.903
12	R_2=R_3=R_4=OH, R_1=H	3.748	0.984	3.772	0.96	3.712	1.02	3.776	0.966	3.748	0.984	3.833	0.899	3.838	0.894	3.822	0.910
13	R_2=R_3=R_4=OCH$_{3,}$ R_1=H	3.739	0.993	3.767	0.965	3.69	1.042	3.769	0.963	3.722	1.01	3.841	0.891	3.837	0.895	3.831	0.901
14	R_2=R_4=C(CH$_3$)$_{3,}$ R_3=OH, R_4=H	3.804	0.928	3.793	0.939	3.755	0.977	3.785	0.947	3.811	0.921	3.818	0.914	3.838	0.894	3.829	0.903

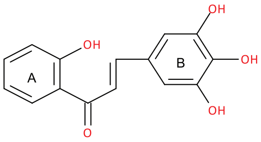
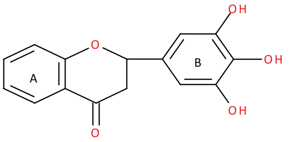
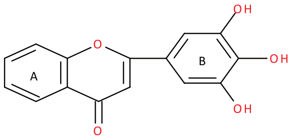
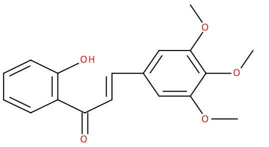
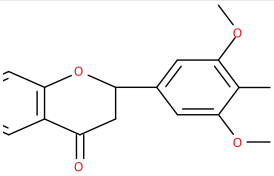
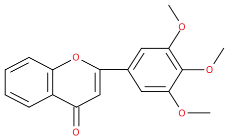
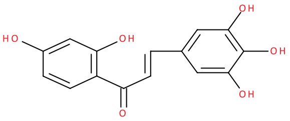
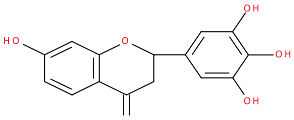
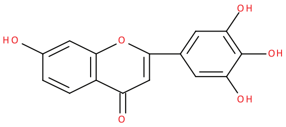
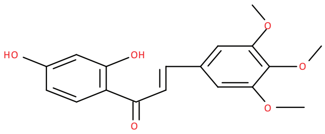
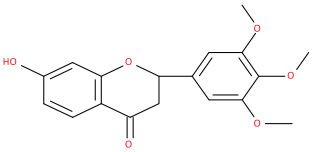
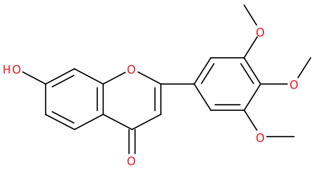
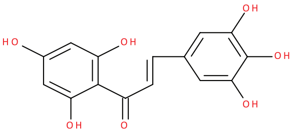
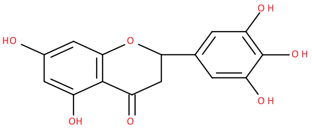
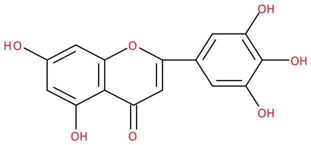
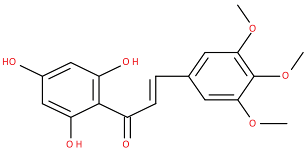
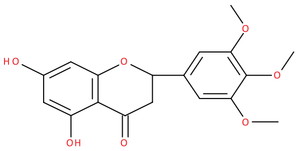
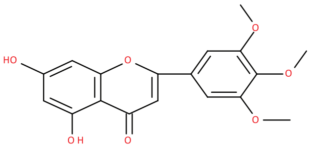
Note: * – Numbering of carbon atoms of the main conjugation chain is given in accordance with the numbers generated by the calculation programs

Table 4 – The values of the bond numbers (Nμ) and free valency indices (Fμ) on the C-1 → C-6 → C-7 → C-8 atoms of the main conjugation chain of 5,7-dihydroxyflavone derivatives

No.	Carbon atoms	C-1		C-2		C-3		C-4		C-5		C-6		C-7		C-8	
	R	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ	Nμ	Fμ
1	$R_1=R_2=R_3=R_4=H$	3.808	0.924	3.851	0.881	3.835	0.897	3.852	0.88	3.809	0.923	3.829	0.903	3.793	0.939	3.701	1.031
2	$R_1=OH$, $R_2=R_3=R_4=H$	3.759	0.973	3.785	0.947	3.832	0.9	3.837	0.895	3.807	0.925	3.724	1.008	3.782	0.950	3.712	1.02
3	$R_1=OCH_3$, $R_2=R_3=R_4=H$	3.769	0.963	3.77	0.962	3.834	0.898	3.834	0.898	3.81	0.922	3.739	0.993	3.793	0.939	3.712	1.02
4	$R_2=OH$, $R_1=R_3=R_4=H$	3.745	0.987	3.798	0.934	3.771	0.961	3.848	0.884	3.797	0.935	3.837	0.895	3.798	0.934	3.707	1.25
5	$R_2=OCH_3$, $R_1=R_3=R_4=H$	3.738	0.994	3.8	0.932	3.767	0.965	3.848	0.884	3.795	0.937	3.838	0.894	3.796	0.936	3.705	1.027
6	$R_3=OH$, $R_1=R_2=R_4=H$	3.805	0.927	3.789	0.943	3.769	0.963	3.774	0.958	3.805	0.927	3.798	0.934	3.787	0.945	3.694	1.038
7	$R_3=OCH_3$, $R_1=R_2=R_4=H$	3.808	0.924	3.783	0.949	3.771	0.961	3.771	0.961	3.805	0.927	3.794	0.938	3.783	0.949	3.691	1.041
8	$R_2=R_3=OH$, $R_1=R_4=H$	3.746	0.986	3.784	0.948	3.742	0.99	3.794	0.938	3.796	0.936	3.820	0.912	3.793	0.939	3.700	1.032
9	$R_2=OCH_3$, $R_3=OH$, $R_1=R_4=H$	3.738	0.994	3.781	0.951	3.738	0.994	3.793	0.939	3.796	0.936	3.819	0.913	3.790	0.942	3.698	1.034
10	$R_2=OH$, $R_3=OCH_3$, $R_1=R_4=H$	3.749	0.983	3.788	0.944	3.746	0.986	3.79	0.942	3.796	0.936	3.816	0.916	3.789	0.943	3.697	1.035
11	$R_2=R_3=OCH_3$, $R_1=R_4=H$	3.741	0.991	3.775	0.957	3.743	0.989	3.788	0.944	3.796	0.936	3.816	0.916	3.787	0.945	3.697	1.035
12	$R_2=R_3=R_4=OH$, $R_1=H$	3.737	0.995	3.776	0.956	3.709	1.023	3.771	0.961	3.732	1.0	3.825	0.907	3.797	0.935	3.705	1.027
13	$R_2=R_3=R_4=OCH_3$, $R_1=H$	3.723	1.009	3.771	0.961	3.689	1.043	3.773	0.959	3.71	1.022	3.833	0.899	3.791	0.941	3.704	1.028
14	$R_2=R_4=C(CH_3)_3$, $R_3=OH$, $R_4=H$	3.785	0.947	3.794	0.938	3.742	0.99	3.787	0.945	3.79	0.942	3.795	0.937	3.777	0.955	3.689	1.043

Note: * – Numbering of positions in accordance with figures generated by settlement programs

Table 5 – Comparative quantum-chemical characteristics of the C-8 atom of 2’-hydroxy-, 2’, 4’-dihydroxy- and 2’,4’,6’-threehydroxychalcones derivatives containing substituents in positions 3, 4, 5 of the ring “*B*”*

			
a.e.	–0.3016	–0.4337	–0.4337
Nμ	3.817	3.815	3.815
Fμ	0.915	0.917	0.917
El.d.	4.3195	4.3737	4.4337
			
a.e.	–0.3136	–0.4370	–0.4370
Nμ	3.813	3.821	3.821
Fμ	0.919	0.911	0.911
El.d.	4.3136	4.4370	4.437
			
a.e.	–0.3013	–0.4342	–0.4158
Nμ	3.818	3.816	3.699
Fμ	0.914	0.916	1.033
El.d.	4.3013	4.4343	4.4158
			
a.e.	0.3130	–0.4378	–0.4495
Nμ	3.815	3.821	3.686
Fμ	0.917	0.911	1.046
El.d.	4.3113	4.4378	4.4495
			
a.e.	–0.3115	–0.4252	–0.4170
Nμ	3.784	3.822	3.705
Fμ	0.948	0.91	1.027
El.d.	4.3115	4.4253	4.4170
			
a.e.	–0.3265	–0.4291	–0.4190
Nμ	3.820	3.831	3.704
Fμ	0.912	0.901	1.028
El.d	4.3266	4.4292	4.4190

Note: * – Numbering of positions in accordance with figures generated by settlement programs

The most characteristic features are recorded in compounds 12x and 13x, where ring "B" is represented by the remainder of pyrogallol or its fully methylated derivative. This arrangement of hydroxy groups is characteristic of natural flavonoids – myricetin, tricetin and tricin [1,2,3], which are the most active antioxidants [10] with respect to OH radical. Atoms C-1, C-2, C-5, C-8 are characterized by approximately the same values of Nµ and Fµ for both 12x and 13x (Table 2).

There is a very important feature: the carbon atoms on the «B» ring, to which the electron-donating OH and OCH_3 groups are bound with, are characterized by a positive charge (C-1 for 2x and 3x; C-2 for 4x and 5x; C-3 for 6x, 7x, 8x, 9x, 10x, 11x, 12x and 14x; C-4 at 8x, 9x, 10x, 11x, 12x, 13x).Table 2 shows that the carbon atoms listed above, are characterized by rather high values of the free valence indices, however, the presence of a positive charge on these atoms precludes the addition of an electrophilic hydroxyl radical to them at the initial stage.

5,7-dihydroxyflavanone derivatives

Table 3 shows the values of Nµ and Fµ for the analyzed flavanones. Comparing them with similar characteristics for chalcones (Table 2), it can be notified that flavanones have bond numbers and, accordingly, free valence indices, not fundamentally different from those of chalcones.

In flavanones 12anone and 13anone on C-1, C-3, C-5 atoms, the values of Fµ are very close or equal to 1.0, which indicates the predisposition of the indicated positions of the ring "B" to the attachment, possibly, by the radical mechanism.

The values of the free valence indices of C-6, C-7 and C-8 atoms also indicate the ability of these atoms to addition reactions.

5,7-dihydroxyflavone derivatives

It should be notified that in this group of derivatives, the C-7 carbon atom is characterized by a positive Mulliken charge in all compounds, without exception.

There is a similar pattern for atoms C-2 (compounds 4, 5, 9, 10–13one), C-3 (compounds 6–12one and 14one) and C-4 (compounds 12one and 13one).

The presence of a positive charge on carbon atoms in these positions indicates that at the initial stage, the addition of an electrophilic hydroxyl radical to the listed carbon atoms is excluded.

At the same time, the C-8 position is characterized by such features as low bond numbers (Nµ = 3.689–3.712) in comparison with other carbon atoms in combination with rather high free valence indices (Fµ = 1.02–1.25) (Table 4). At the same carbon atom, the negative Mulliken charge is in the range from –0.4122 to –0.4508.

Thus, the C-8 position is the most probable center where the radical OH should join.

It is clear that the interaction of an attacking particle with a given carbon atom of the vinylene group will entail a redistribution of the electron plane, bond numbers, Mulliken charge and free valence indices. This, in turn, will lead to the formation of new nucleophilic centers, where the subsequent ·OH radical will join, and so on until the carbon atoms in the flavone transformation products become extremely saturated. Every time, this can be judged by the changing values of the bond numbers, free valence indices, as well as the charges of carbon atoms and their electron density.

Such an approach, in our opinion, predetermines a quantitative assessment of the ratio of the moles number of the OH radical to 1 mole of the initial flavone during their interaction.

Table 5 shows the comparative quantum chemical characteristics of C-8 atoms in the analyzed groups of chalcones, flavanones and flavones containing electron-donating substituents in the rings "A" and "B". The choice of the compounds containing three -OH and -OCH_3 groups (pyrogallol type of substitution) is determined, first of all, by their greatest antioxidant and anti-inflammatory kinds of activity, which was experimentally proved [10–12].

It follows from the table that, when passing from chalcones to flavones, the bond numbers (Nµ) decrease, which entails an increase in the values of the free valence indices (Fµ). That indicates an increase in the reactivity of the C-8 atom with respect to the electrophilic hydroxyl radical.

CONCLUSION

The article is devoted to the analysis of the quantum-chemical parameters of chalcones, flavanones and flavones, in which the "A" ring is represented by the phloroglucinic type, and the "B" ring of all the three groups of compounds in the same positions, contains electron-donating –OH and –OCH_3 groups.

In all the three compounds –14x, 14anone and 14one – the "B" ring contains two *tert*-butyl substituents and a phenolic hydroxyl between them (see Table 1), i.e. the "B" ring is a spatially hindered phenol which, due to the homolytic cleavage of the OH bond, is able to form a stable phenoxyl radical that actively interacts with the hydroxyl radical.

For the carbon atoms of the main conjugation chain C-1 → C-6 → C-7 → C-8, free valence indices (Fµ) have been found.

It has been established that the OH group in position 6′ of the "A" ring of chalcones, and in position 5 of the "A" ring of flavanones and flavones, has conflicting effects on the bond numbers: when passing from chalcone to flavanone, Nµ increases, and then, in flavone, sharply decreases. Using the dependence Fµ = Nmax – Nµ, the corresponding free valency indices have been found out; for the C-8 atoms of all flavone derivatives, they correspond to the expression Fµ≥1.

With reference to the previous reports and taking into consideration both the Mulliken charge (a.u.) and the electron density on this atom, the following conclusion has been confirmed: at the initial stage of the reaction the electrophilic hydroxyl radical is attached at the C-8 position of the cinnamoyl fragment.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

E.T. Oganesyan – search and analysis of literature, interpretation of results, writing the text of the manuscript;
S.S. Shatokhin – search and analysis of literature, performance of quantum-chemical calculations, interpretation of the results

REFERENCES

1. Karrer W. Konstitution and Vorkommen der organischen Pflanzenstoffe Birkhäuser, BaselBasel. 958;12:1216. DOI: 10.1007/978-3-0348-6808-2.
2. Litvinenko VI. Prirodnye flavonoidy. V knige «Tekhnologiya i standartizaciya lekarstv». – Har'kov: OOO «RIREG». 1996:784. Russian
3. Klyshev LK, Bandyukova VA, Alyukina LS. Flavonoids of plants, Alma-Ata, "Science". 1978:220. Russian
4. Tarakhovsky YuS, Kim YuA, Abrasilov BS, Muzafarov EN. Flavonoids: biochemistry, biophysics, medicine. Synchrobok: Pushchino. 2013:310. Russian
5. Oganesyan ET, Shatokhin SS, Glushko AA. Use of quantum-chemical parameters for predicting the antiradical (HO·) activity of related structures containing a cinnamic mold fragment. I. Derivatives of cinnamic acid, chalcon and flavanon. Pharmacy and pharmacology. 2019;7 (1):53–66. DOI: 10.19163/2307-9266-2019-7-1-53-66.
6. Oganesyan E.T., Shatokhin S.S. Using quantum-chemical parameters for predicting anti-radical (HO·) activity of related structures containing a cinnamoyl fragment II. Derivatives of 2',4'-dihydroxychalcone, flavanone and flavone, containing a hydroxy group in position 7. Pharmacy & Pharmacology. 2020;8(2):112–123. DOI: 10.19163/2307-9266-2020-8-2-112-123.
7. Minkin VI, Simkin BYa, Minyaev RM. Structure of molecules. Rostov-on-Don: Phenix. 1997: 560. Russian
8. Zhdanov Yu.A. The theory of the structure of organic compounds. Moscow: "High School". 1971: 288 p. Russian
9. Krasnov KS. Molecules and chemical bonds. Moscow: "High School". 1977:280. Russian
10. Nikol'skij BP. Spravochnik himika. T. 3. Himicheskoe ravnovesie i kinetika. Svojstva rastvorov. Elektrodnye processy. 2edth. Leningrad: Himiya. 1964: 1005. Russian
11. Oganesyan ET, Maltsev YuA, Tvorovsky DE. Investigation of the reaction mechanism of flavone derivatives with a hydroxyl radical by semi-empirical methods. Journal of General Chemistry. 2001;71(6):999–1005. Russian
12. Oganesyan ET, Dorkina EG, Khochaeva MR, Tuskaev VA, Maltsev YuA. The use of quantum chemical methods to substantiate the antiradical (OH) action of polyhydroxychalcones. Chemical-Pharmaceutical Journal. 2002;36(12): 21–25. Russian

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