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ОРИГИНАЛЬНАЯ СТАТЬЯ

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USING QUANTUM-CHEMICAL PARAMETERS FOR PREDICTING ANTIRADICAL (HO•) ACTIVITY OF RELATED STRUCTURES CONTAINING A CINNAMOIL FRAGMENT. IV. STRUCTURE-ACTIVITY RELATIONSHIP BETWEEN UNSATURATION INDICES AND FLAVONE DERIVATIVES WITH FLOROGLUCIN RING "A"

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The quantum-chemical parameters of 52 derivatives related to flavanones, flavanonoles, flavones and flavonoles with a phloroglucinic type of the A ring and containing electron-donating substituents in the B ring were studied.

The aim is the analysis of the dynamics of changes in the electron density, bond numbers, free valence indices and unsaturation indices on carbon atoms C-7→C-8 of the vinyl group of the main conjugation chain in relation to the position and number of substituents in the "B" ring and the type of the pharmacological activity.

Materials and methods. The quantum-chemical parameters of the 4 analyzed groups of the compounds, have been calculated by the semi-empirical method PM7 (WinMopac 2016 program) on the workstation with an Intel Xeon E5-1620 3.5 GHz processor, 20 GB of RAM.

Results and discussion. When comparing the quantum chemical parameters of the analyzed compounds, it was established that when the C-7→C-8 multiple bond is formed, the free valency and unsaturation indices increase on both carbon atoms of the vinylene group in flavones and flavonols compared to the corresponding flavanones and flavanonols. This is explained by the fact that the value of the bond numbers Nμ on these atoms, on the contrary, decreases (Fμ = 4.732-Nμ). The transition from flavanone to flavone is accompanied by the formation of a vinyl group C-7→C-8, and therefore both atoms from the sp^3-hybridized state go into the sp^2-state. The consequence of this transformation is a change in the electronegativity value and an increase in the unsaturation index of C-7 and C-8 atoms: C sp^3 = 2.5; Csp^2 = 2.8. At the same time, the transition from flavanone to flavone leads to the formation of a conjugated system with the participation of π-electrons of the aromatic system "B", C-7, C-8 atoms and the carbonyl group, which is commonly called the "main conjugation chain". These structural changes, namely, the transition from a less oxidized flavanone to a more oxidized flavone, contribute to a decrease in the electron density on C-7 and C-8 atoms, and an increase in the total unsaturation of the molecules in general. Mulliken charges on C-7 of all groups of compounds are characterized by a positive value. As for the carbon atoms of the B fragment, the following features are revealed here: in the presence of one substituent –OH or –OCH_3 on the carbon atom to which the substituent is bounded, the Mulliken charge is positive; if there are two substituents in the B ring –OH or –OCH_3, as well as two -OCH_3 groups, then the carbon atoms bonded to the indicated substituents also have a positive Mulliken charge; in the case of trihydroxy substituted in the C-2, C-3 and C-4 B ring, all three carbon atoms are characterized by a positive Mulliken charge; if there are methoxy groups in positions C-2, C-3 and C-4, then the positive Mulliken charge is concentrated only on C-2 and C-4 atoms, and on C-3 atom this charge has a negative value.

Conclusion. The above data on the quantum-chemical parameters of the main conjugation chain indicate that the transition of C-7 and C-8 atoms to the sp^2-hybrid state, leads to a decrease in the electron density and a decrease in the bond numbers, with a simultaneous increase in the indices of unsaturation and free valence on these atoms. Thus, the trigger mechanism of the anti-radical activity, primarily with respect to the HO• radical, is determined by the fact that this particle, electrophilic in its properties, will attach in the C-8 atom during an initial attack.

Keywords: flavanones, flavanonoles, flavones, flavonoles, phloroglucinic type of the A ring

Abbreviations: Fμ – free valence indices; IUA – unsaturation index; EO – electronegativity; Nμ – the total values of the bond numbers; Vμ – theoretical valence.

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ИСПОЛЬЗОВАНИЕ КВАНТОВО-ХИМИЧЕСКИХ ПАРАМЕТРОВ ДЛЯ ПРОГНОЗИРОВАНИЯ АНТИРАДИКАЛЬНОЙ (HO•) АКТИВНОСТИ РОДСТВЕННЫХ СТРУКТУР, СОДЕРЖАЩИХ ЦИННАМОИЛЬНЫЙ ФРАГМЕНТ. IV. ВЗАИМОСВЯЗЬ СТРУКТУРА-АКТИВНОСТЬ МЕЖДУ ИНДЕКСАМИ НЕНАСЫЩЕННОСТИ И ПРОИЗВОДНЫМИ ФЛАВОНА С ФЛОРОГЛЮЦИНОВЫМ КОЛЬЦОМ «А»

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Изучены квантово-химические параметры 52 производных, относящихся к флаванонам, флаванонолам, флавонам и флавонолам с флороглюциновым типом кольца «А», и содержащими электронодонорные заместители в кольце «В».
Цель. Анализ динамики изменения электронной плотности, связевых чисел, индексов свободной валентности и ненасыщенности на атомах углерода С-7→С-8 виниленовой группы главной цепи сопряжения во взаимосвязи с положением и числом заместителей в кольце «В» и видом фармакологической активности.
Материалы и методы. Квантово-химические параметры анализируемых 4-х групп соединений рассчитаны полуэмпирическим методом PM7 (программа WinMopac 2016) на рабочей станции с процессором IntelXeonE5-1620 3,5 ГГц, 20 Гб оперативной памяти.
Результаты и обсуждение. При сопоставлении квантово-химических параметров анализируемых соединений установлено, что при формировании кратной связи С-7→С-8 индексы свободной валентности и ненасыщенности возрастают на обоих углеродных атомах виниленовой группы у флавонов и флавонолов по сравнению с соответствующими флаванонами и флаванонолами. Это объясняется тем, что величина связевых чисел Nμ на этих атомах, наоборот, уменьшается (Fμ= 4,732-Nμ). Переход от флаванона к флавону сопровождается формированием виниленовой группы С-7→С-8, в связи с чем оба атома из sp^3-гибридизованного состояния переходят в sp^2-состояние. Следствием такой трансформации является изменение значения электроотрицательности и увеличением индекса ненасыщенности атомов С-7 и С-8: С sp^3=2,5; С sp^2=2,8. Вместе с тем переход от флаванона к флавону приводит к образованию сопряженной системы с участием π-электронов ароматического ядра «В», атомов С-7, С-8 и карбонила что принято называть «главной цепью сопряжения». Указанные структурные изменения, а именно, переход от менее окисленного флаванона к более окисленному флавону способствует уменьшению электронной плотности на атомах С-7 и С-8, и увеличению суммарной ненасыщенности молекул в целом. Малликеновские заряды на С-7 всех групп соединений характеризуются положительным значением. Что касается атомов углерода фрагмента «В», то здесь выявлены следующие особенности: при наличии одного заместителя –ОН или $–OCH_3$ на атоме углерода, с которым связан заместитель, Малликеновский заряд – положительный; если в кольце «В» имеются два заместителя –ОН или $–OCH_3$, а также две $–OCH_3$ группы, то атомы углерода, связанные с указанными заместителями, тоже имеют положительный Малликеновский заряд; в случае тригидроксизамещенных у С-2', С-3' и С-4' кольца «В» все три атома углерода характеризуются положительным Малликеновским зарядом; если в положениях С-2', С-3' и С-4' находятся метоксигруппы, то положительный Малликеновский заряд сосредоточен только на атомах С-2' и С-4', а на С-3' этот заряд имеет отрицательное значение.
Заключение. Перечисленные выше данные о квантово-химических параметрах главной цепи сопряжения свидетельствуют о том, что переход атомов С-7 и С-8 в sp^2-гибридное состояние приводит к понижению электронной плотности и уменьшению величин связевых чисел, при одновременном увеличении индексов ненасыщенности и свободной валентности на этих атомах. Таким образом, пусковой механизм антирадикальной активности, в первую очередь в отношении радикала HO•, определяется тем, что эта электрофильная по своим свойствам частица при первичной атаке присоединится по положению С-8.
Ключевые слова: флаваноны; флаванонолы; флавоны; флавонолы; флороглюциновый тип кольца «А»
Список сокращений: Fμ – индексы свободной валентности; IUA – индекс ненасыщенности; ЭО – электроотрицательность; Nμ – суммарные значения связевых чисел; Vμ – теоретическая валентность.

INTRODUCTION

The final IV-th report summarizes the results of the study of the relationship between the structure of the compounds containing the phloroglucinic type A ring and electron-donating substituents in the B ring with total unsaturation indices (IUA) and electron density.

THE AIM of the article is the analysis of the dynamics of changes in the electron density, bond numbers, free valence indices and unsaturation indices on carbon atoms C-7 → C-8 of the vinyl group of the main conjugation chain in relation to the position and number of substituents in the "B" ring and the type of the pharmacological activity.

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MATERIALS AND METHODS

The quantum-chemical parameters of the 4 analyzed groups of the compounds, have been calculated by the semi-empirical method PM7 (WinMopac 2016 program) on the workstation with an Intel Xeon E5-1620 3.5 GHz processor, 20 GB of RAM.

RESULTS AND DISCUSSION

The structures of the analyzed compounds and the total values of the listed parameters in C-1→C-9 section of the cinnamoyl fragment are presented in Table 1.

It follows from the Table that, when switching from flavanones to flavanonols, the values of the free valency (Vμ) and unsaturation indices (IUA) change very slightly (the second decimal place is ~0.04) despite the fact that on flavanonol C-8 atom the electron-donating OH-group appears; it contributes to an increase in the electron density on C-7 and a decrease onC-8.

In the flavone-flavonole pair, the introduction of phenolic hydroxyl on C-8 promotes a clear increase in the IUA value, an increase in the electron density on C-7, and its decrease on C-8.

The Vμ value remains almost unchanged, including that of the flavanone-flavanonole pair.

This feature is preserved in all types of compounds presented in Table 1, and for this reason, we will not consider the Vμ parameter further.

After the publication of the pioneering studies of Szent-Györgyi in 1936 about the biological properties of certain flavonoids, the whole subsequent period made it possible to accumulate the extensive information about representatives of this class of natural compounds.

Currently, the structure of approximately 8000 flavonoids [1-6] has been described, and only a very small number of individual substances (approximately 2–3%) from this variety of aglycones and glycosides has been studied in detail from biochemical and pharmacological points of view. Such a low percentage of available information can be explained by the fact that in the absolute majority of plants the content of individual substances is scanty (0.1–2%) and their production in sufficient quantities for the purpose of subsequent biochemical and pharmacological studies is associated with high material costs.

As a rule, detailed information about the biological properties of individual compounds – derivatives of 2-phenyl-benz-γ-pyrone – concerns the substances that can be obtained preparatively from the raw materials (quercetin and rutin from Sophora Japonica, buckwheat herb; taxifolin, or dihydroquercetin, from Lárix sibírica; hesperitin and hesperidin – from the pulp – the spongy part of citrus peels; diosmin – by the oxidation of hesperitin, etc.).

Nevertheless, the most characteristic and perhaps most important are considered the antioxidant properties of flavonoids, the indirect effect of which is manifested by about 50 types of pharmacological activity [7–10].

It should be notified that throughout its evolutionary development, the persons using plant foods, introduce flavonoids into their bodies, and they protect the cells from the oxidative stress and thereby normalize their metabolism.

Thus, flavonoids are a kind of a protective shield of the body's natural antioxidant system, and this is important for preserving the entire cellular system.

The currently used therapeutic and preventive agents based on flavonoids are their total substances – legalon, karsil, silibor, flacumin, etc. (most often) – or individual compounds: rutin, quercetin, flaronin, etc[1]. This treatment is represented not by immediate action drugs, therefore their therapeutic effect is manifested, as a rule, during a long-term administration (detralex, troxevasin). The derivatives of 2-phenyl-benz-γ-pyrone, wide-spread in nature, are represented in the form of glycosides and their aglycones, and glycosides are predominant.

It should be emphasized that the non-carbohydrate residue is a pharmacologically active fragment in flavonoid glycosides, i.e. aglycone, therefore, there is no need to discuss the enormous economic costs that would be necessary for a detailed study of the biological properties of at least one hundred aglycones – derivatives of 2-phenylbenz-γ-pyrone. Such an activity is unproductive, because it is unlikely that new properties of these compounds should be revealed. Moreover, if we compare the known data on the biological activity of the studied flavonones, flavonols and flavononols with the PASS prediction data [11], the most common types of activity for all types of structures are anti-inflammatory, antioxidant, hepatoprotective, choleretic. Besides, they are characterized by such properties as free radical binding, antimutagenic, capillary strengthening and act as apoptosis agonist, membrane integrity agonist, membrane permeability inhibitors.

Individual compounds can be replaced by total flavonoid substances obtained from the corresponding producing plants, because the effect is often preserved, and sometimes exceeds the expected result.

The data about the antiradical (HO•) activity of flavonoids are disorganized and, as a rule, few. Moreover, in the works that are not interconnected, the authors use different methods for generating this radical, which does not make it possible to quantify and compare the results obtained.

The most informative are the works [12] and [13], which provide information on the activity of the representative groups of the compounds.

[1] State Register of Medicines. Available from: https://grls.rosminzdrav.ru/Default.aspx

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Table 1 – The total values of Nμ (bond numbers), Vμ (theoretical valency), IUA (unsaturation index) and electron density on carbon atoms of the main conjugation chain (C-1→C-9)

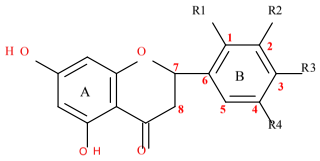
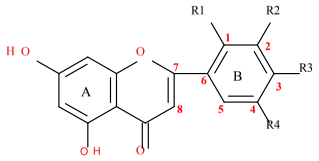
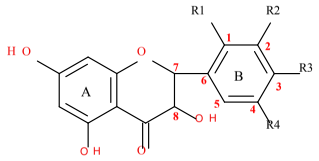
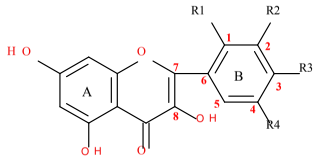
N	Substituents				 Flavanone 1				 Flavone 2				 Flavanonole 3				 Flavonole 4			
	R_1	R_2	R_3	R_4	Nμ	Vμ	IUA	Эл.пл.	Nμ	Vμ	IUA	Эл.пл	Nμ	Vμ	IUA	Эл.пл	Nμ	Vμ	IUA	Эл.пл
1	H	H	H	H	34.48	35.53	1.05	36.502	34.24	35.5	1.27	36.287	34.41	35.51	1.09	36.208	34.18	35.56	1.38	36.059
2	OH	H	H	H	34.24	35.4	1.15	36.27	34.00	35.34	1.34	36.021	34.17	35.36	1.19	35.906	33.95	35.41	1.46	35.787
3	CH_3O	H	H	H	34.28	35.45	1.16	36.252	34.02	35.37	1.36	36.083	34.17	35.38	1.21	35.932	34.02	35.5	1.49	35.828
4	H	OH	H	H	34.24	35.4	1.16	36.297	34.06	35.44	1.38	36.049	34.2	35.5	1.3	35.965	33.99	35.45	1.49	35.821
5	H	CH_3O	H	H	34.23	35.42	1.19	36.337	34.05	35.45	1.41	36.091	34.19	35.42	1.23	36.001	33.68	35.5	1.82	35.861
6	H	H	OH	H	34.22	35.38	1.15	36.273	33.98	35.33	1.35	36.033	34.18	35.37	1.19	35.942	33.94	35.4	1.47	35.798
7	H	H	CH_3O	H	34.22	35.39	1.16	36.314	33.96	35.34	1.38	36.076	34.17	35.39	1.19	35.979	33.92	35.42	1.5	35.839
8	H	OH	OH	H	34.14	35.41	1.26	36.025	33.93	35.41	1.48	35.786	34.1	35.4	1.3	35.691	33.88	35.47	1.59	35.552
9	H	CH_3O	OH	H	34.13	35.42	1.29	36.057	33.91	35.42	1.51	35.823	34.09	35.42	1.33	35.728	33.86	35.48	1.62	35.588
10	H	OH	CH_3O	H	34.14	35.42	1.28	36.057	33.93	35.42	1.49	35.823	34.1	35.41	1.32	35.724	33.87	35.48	1.61	35.587
11	H	CH_3O	CH_3O	H	34.14	35.42	1.29	36.084	33.9	35.43	1.53	36.861	34.09	35.43	1.34	35.764	33.85	35.49	1.64	35.624
12	H	OH	OH	OH	33.98	35.318	1.33	35.786	33.81	35.37	1.56	35.547	33.95	35.32	1.37	35.45	33.75	35.42	1.67	35.312
13	H	CH_3O	CH_3O	CH_3O	33.93	35.32	1.39	35.898	33.75	35.37	1.62	35.661	33.9	35.33	1.43	35.562	33.7	35.42	1.73	35.425

Table 2 – Antiradical (HO•) activity of some flavone and flavonole derivatives

	Compounds with antiradical (HO•) activity experimentally detected*	Antiradical (HO•) activity established experimentally* A,%	Total values of bond numbers (Nμ), theoretical valency (Vμ), unsaturation indices (IUA) and electron density (E.D.) on carbon atoms of the main conjugation chain			
1	Flavon (unsubstituted)	4	Nμ	Vμ	IUA	E.D.
2	apigenin(5,7,4'-trihydroxyflavone)	34	34.27	35.53	1.26	36.156
3	diosmethine(5,7,3'-trihydroxy-4'-methoxyflavone)	39	33.98	35.33	1.35	36.033
4	5,7-dihydroxy-3', 4', 5'-trimethoxyflavone	28	33.93	35.42	1.49	35.823
5	myricetin (3,5,7,3', 4', 5'-hexahydroxyflavone)	50	33.75	35.37	1.62	35.661
6	quercetin(3,5,7,3', 4'-pentahydroxyflavone)	48	33.75	35.42	1.67	35.312
7	rhamnetin (3,5,3', 4'-tetrahydroxy-7-methoxyflavone)	46	33.88	35.47	1.59	35.552
8	morin (3,5,7,2', 4'-pentahydroxyflavone)	40	33.88	35.474	1.589	35.574
9	kaempferol (3,5,7,4'-tetrahydroxyflavone)	20	33.641	35.173	1.532	35.564
10	Luteolin** (5,7,3',4'-tetrahydroxyflavone)		33.93	35.41	1.48	35.786

Note: * – compounds 1–9 show the data according to Husaine... [12]; **– There is no available data on the radical (HO•) activity

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Table 3 – Predicted PASS Activities

N	Compounds with antiradical (HO•) activity (A,%) experimentally detected according to [11]		Activity	Compounds and their probability of predicted activity								
				1	2	3	4	5	6	7	8	9
1	**Flavanone*** (unsubstituted)	4	Antimutagenic	0.795	0.921	0.943	0.931	0.963	0.940	0.952	0.947	0.948
2	Apigenin	34		0.547	0.64	0.627	0.612	0.720	0.689	0.667	0.680	0.676
3	diosmetin	39			0.732	0.683	0.651	0.924	0.872	0.798	0.850	0.856
4	5,7-dihydroxy-3', 4', 5'-trimethoxyflavone	28	Antiinflammatory		0.719	0.808	0.784	0.832	0.811	0.839	0.759	0.771
	Flavononoles		Antioxidant	0.947	0.967	0.956	0.944	0.968	0.973	0.966	0.974	0.974
5	myricetin	50		0.914	0.946	0.952	0.959	0.959	0.938	0.954	0.956	0.957
6	quercetin	48		0.720	0.847	0.851	0.860	0.915	0.887	0.877	0.886	0.881
7	rhamnetin	46	Freeradicalscavenger	0.539	0.539		0.569			0.529		0.530
8	morin	40			0.650	0.692	0.607	0.705	0.737	0.726		0.705
9	kaempferol	20	Membrane integrity agonist	10	11	12	13	15	16	17	14	18
10	Flavanone (unsubstituted)			0.537	0.857	0.883	0.881	0.917	0.920	0.916	0.910	0.895
11	Naringenin (dihydroapigenin)		Apoptosis agonist	0.602	0.660	0.691	0.640	0.628	0.737	0.692	0.685	0.722
12	Eriodiktiol (dihydroluteolin)			0.550	0.794	0.817	0.746	0.938	0.961	0.919	0.832	0.946
13	Hesperitin (dihydrodiosmetin)		Inhibitor membrane permeability	0.514	0.769	0.809	0.878	0.877	0.901	0.925	0.830	0.831
14	5,7,3', 4', 5'-pentahydroxyflavanone			0.935	0.964	0.962	0.952	0.973	0.969	0.966	0.956	0.975
15	Dihydroquercetin (Taxifolin)			0.748	0.851	0.877	0.874	0.850	0.834	0.848	0.830	0.823
16	Dihydromyretin (ampelopsin)**			0.520	0.709	0.790	0.780	0.795	0.835	0.785	0.800	0.766
17	3,5,7,3'-tetrahydroxy-4'-methoxyflavanone		Capillary fragility treatment	0.712	0.714	0.634	0.653	0.687	0.644	0.706	0.594	0.759
18	Dihydrokaempferol (aromadendrine)				0.510	0.577	0.566	0.714	0.668	0.707	0.690	0.668

Note: * – compounds 2 → 4 are flavone derivatives; ** – Compounds 16–18 are flavanonole derivatives

Table 4 – PASS-predicted types of activity of some flavanones

N	Compounds	Antiviral activity	Antitumoractivity	The total values of the bond numbers (Nμ), theoretical valency (Vμ), unsaturation indices (IUA) and electron density (E.D.) on carbon atoms of the main conjugation chain			
				Nμ	Vμ	IUA	E.D.
1	Flavanone(unsubstituted)	Influenza (0.555) Rhinovirus (0.578)	Antineoplastic (0.578)	34.48	35.53	1.05	36.602
2	Naringenin (dihydroapigenin)	Influenza (0.691) Rhinovirus (0.611)	Antineoplastic (0.751) Anticarcinogenic (0.690)	34.22	35.38	1.15	36.273
3	Hesperitin (dihydrodiosmetin)	Influenza (0.673) Rhinovirus (0.564) Herpes (0.503)	Antineoplastic (0.772) Anticarcinogenic (0.783)	34.14	35.42	1.28	36.057
4	5,7-dihydroxy-3', 4', 5'-trimethoxyflavone	< 0.500	Antineoplastic (0.628) Anticarcinogenic (0.514)	33.93	35.32	1.39	35.898
5	Dihydromyretin (ampelopsin)	Influenza (0.659) Herpes (0.508)	Antineoplastic (0.781) Anticarcinogenic (0.837)	33.95	35.32	1.37	35.45
6	Dihydroquercetin (Taxifolin)	Rhinovirus (0.503) Influenza (0.620)	Antineoplastic (0.790) Anticarcinogenic (0.690)	34.1	35.4	1.3	35.691
7	Dihydrorhamnetin	Rhinovirus (0.510) Influenza (0.625)	Antineoplastic (0.800) Anticarcinogenic (0.695)	34.2	35.42	1.3	35.350
8	3,5,7,2',4'--pentahydrohyflavanone	Herpes (0.543) Hepatit B (0.505)	Antineoplastic (0.808) Anticarcinogenic (0.796)	34.35	35.42	1.33	35.921
9	Dihydrokaempferol (aromadendrine)	Rhinovirus (0.528) Influenza (0.617)	Antineoplastic (0.715) Anticarcinogenic (0.792)	34.18	35.37	1.19	35.942
10	Eriodiktiol (dihydroluteolin)	Rhinovirus (0.590)	Antineoplastic (0.763) Anticarcinogenic (0.775)	34.14	35.41	1.26	36.025
11	3,5,7,3'-tetrahydroxy-4'-methoxyflavanone	Influenza (0.573)	Antineoplastic (0.747) Anticarcinogenic (0.835)	34.1	35.41	1.32	35.724

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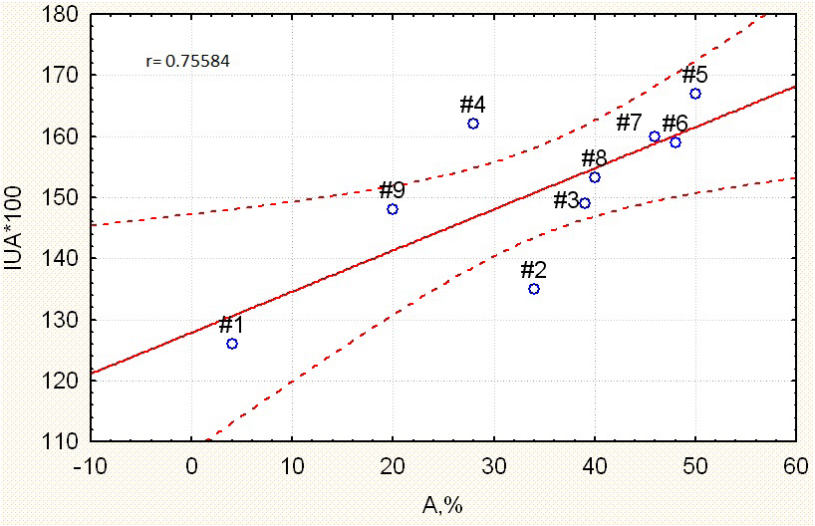

Figure 1 – Functional relationship between $\sum_{IUA}$ of the cinnamoyl fragment of compounds 1–9 (Table 2) and the level of their antiradical activity (HO•)

In the article of Husaine et al. [12], the antiradical activity of nine flavone derivatives (Table 2) which are aglycones, has been studied on the same model. As the data of the table show, myricetin is the most active. It is followed by quercetin, rhamnetin and morin with a slight lag. All four aglycons belong to flavonols, however, if the first three substances in the B ring contain an *ortho*-dihydroxy group in position 3', 4' (the activity is 50, 48, 46, respectively), in morin the hydroxy groups in the B ring are on C-2' and C-4', which, apparently, affects its activity.

Kaempferol, also related to flavonoles, contains only one –OH group in position 4', that's why it has a low activity, which is 2.5 times less than that of myricetin.

Apigenin and diosmetin are not flavonols: in positions 5 and 7 they contain hydroxy groups, and apigenin has one –OH group on C-4', and diosmetin has 3 -OH and 4'-OCH_3 groups in the B ring. The unsubstituted flavone has a minimum activity, it is 4. Although the information presented in [12] is very limited, while comparing these data it can be argued that the antiradical activity of flavonols is higher than that of flavones; the ortho-substitution in the "B" ring of types 3', 4'-diOH or 3'-OH, 4'-OCH_3, enhances the antiradical activity.

In order to expand information about other types of biological activity of the compounds shown in Table 2 and their corresponding flavanone derivatives, the PASS program was used [11]. It allowed to identify other types of activity shown in Tables 3 and 4. Only the species with a probability of occurrence of at least 0.5, are listed here.

The obtained data indicate that for the analyzed derivatives of flavone and flavanone, the most characteristic types of activity are those that were experimentally detected at different times.

The flavonoids listed in Table 4, are also characterized by anticancer (Antineoplastic, Anticarcinogenic, Cytoprotectant) types of activity.

Having such extensive information about various types of biological activity, the functional relationships between one of the quantum-chemical parameters and their levels of activity should be studied. Unfortunately, it is incorrect to identify correlation relationships among such a limited number of compounds that differ in the presence of enol hydroxyl on C-3, because of the 9 compounds, 4 are represented by flavones and 5 by flavonoles.

Special mention should be made about the prognosis of the antiviral activity (Table 4) of the analyzed structures in which the A core is represented by a phloroglucinol fragment: almost all compounds are characterized by the activity against the influenza virus and rhinovirus. Some compounds have activity against the Herpes virus and Hepatitis B virus.

Nowadays and in the near future, the relevant objective will be to find prophylactic drugs against various coronavirus infections. In this regard, the studies using computer technologies, in particular molecular docking, are of particular importance.

The work of Wu et al. [14] presents the results of a study of some natural compounds with antiviral and anti-inflammatory effects. A high affinity of binding to 3CLpro of flavonoids such as chrysin 7-O-glucuronide, hesperidin and neoheperidine has been established. The data obtained indicate that these compounds can be potential inhibitors of 3CLpro and, probably, can be used for the prevention and treatment of infections caused by SARS-CoV2. Likoflavonol (from Glycyrrhizauralensis), cosmosin and mangosteen (from Gurciniamangostana) have also shown similar activities. Moreover, hesperidin can interfere with the interaction of ACE2 with RBD.

The authors have also revealed a high binding affinity of vogonin-7-glucuronide (vagonoside) and vitexin (8-C-glucopyranosidapigenin) with three proteins – Nsp1, Nsp3 and ORF7, which are virulence factors of this

type of coronavirus. The authors have also shown that the highest affinity (of the 3,500 compounds analyzed) for various target proteins is shown by antibacterial, anti-inflammatory and antiviral substances including silybin, hesperidin, neohesperidin, baikalin, campferol-3-rutinoside and rutin. This fact shows that these compounds may be useful for the treatment of SARS-CoV-2 [15–17].

From our point of view, specialist virologists with the appropriate possibilities should pay attention to natural polyphenolic compounds that contain *ortho*-dihydroxy groups in the Baromaticcore. Such substances include caffeic acid, taxifolin (dihydroquercetin), amielopsin (dihydromyreticin), rhamnetin, morin, luteolin, fisetin, robinetin, etc. Of course, it is unlikely that from an economic point of view, in the future, these individual compounds will be available in sufficient quantities.

Earlier, a few our works devoted to the analysis of the quantum chemical characteristics of cinnamic acid derivatives in relation to their antiradical (OH·) activity [13] and possible metabolic pathways, were published. The data obtained were the basis for the prediction and subsequent synthesis of a new derivative of cinnamic acid, which was more active than ascorbic acid (C1/2 = 27.5 μM), caffeic acid (C1/2 = 15.7 μM) by the ability to inhibit the generation of a superoxide anion radical. The resulting new compound (C1/2 = 9.8 μM) is a spatially hindered phenolic OH group located between two *tert*-butyl substituents and is 4-hydroxy-3,5-di-*tert*-butyl cinnamic acid. [18] It is also shown here that there is a linear relationship between the level of antioxidant activity and the total degree of unsaturation of the studied derivatives of cinnamic acid with a correlation coefficient of 0.911.

CONCLUSION

The remainder of cinnamic acid in the structure of flavonoids constitutes the main conjugation chain and, as our studies have shown, the quantum chemical characteristics of the substituted cinnamic acid practically coincide with those of the cinnamic fragment of flavones, flavonoles and flavanones with similar substituents and with the same type of substitution in the B ring [19].

Despite a small number of the related structures in Table 2 (1-4-flavones, 5-9 flavonoles), a linear relationship is observed between the total amount of unsaturation and the type of activity; compounds 2, 3, 5, 6, 7, 8 are located on a straight line (Fig. 1).

The graph indicates that the correlation coefficient is 0.75, it is quite acceptable for biological experiments [20].

Based on the analysis and comparison of the quantum-chemical parameters presented in [13, 18–19], we believe that the unsaturation index (IUA) may be the most reliable criterion for performing correlation analyzes of the antiradical activity (OH•) in the ranks of derivatives of flavone, flavanone, flavonole and flavonole. It is possible, first of all, because the hydroxyl radical, characterized by high electrophilicity, is attached in the C-8 position of the cinnamic fragment[2], where the highest electron density is concentrated.

Nevertheless, this parameter is also convenient for a qualitative analysis of patterns of the structure-activity.

It should be also notified that the transition of the flavone nucleus to flavanone is accompanied by the reduction of the vinylene fragment C-8→C-7 and, accordingly, the C-8 and C-7 atoms pass into the sp^3-hybridized state. Quantum-chemical parameters change as follows: the total values of the bond numbers (Nμ) for flavanones increase, the theoretical valency remains unchanged, the electron density also increases, and the unsaturation index for flavanones decreases compared to the corresponding flavones.

The latest studies on the search for the so-called small molecules able of binding to the coronavirus S-protein, deserve special attention. They will apparently be useful both for prevention and, possibly, for alleviating the infection caused by COVID-19.

Eriodiktiol, chrysin, rutin, hesperidin, quercetin, neohesperidin and others containing the phloroglucinic type of the A ring, as well as ortho-dihydroxy or ortho-methoxy-hydroxy substituents in the B ring, were referred to such “small molecules” by the authors.

Finally, it is possible to carry out chemical modification by introducing specific functional groups into the molecule, depending on the ultimate goal of a synthetic chemist, in case the structure of aglycon, flavonoid and their biochemical and pharmacological properties are known.

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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.

[2] The numeration of carbon atoms of the cinnamoyl fragment generated by WinMopac 2016 program, is kept to.

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