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USING QUANTUM-CHEMICAL PARAMETERS FOR PREDICTING ANTI-RADICAL (HO·) ACTIVITY OF RELATED STRUCTURES CONTAINING A CINNAMIC MOLD FRAGMENT.
I. DERIVATIVES OF CINNAMIC ACID, CHALCON AND FLAVANON

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45 compounds uniting 3 groups of derivatives of cinnamic acid, chalcone and flavanone, have been studied. Each of them includes 15 substances. The analyzed compounds contain a common structural fragment, which is a cinnamic acid residue (cinnamoyl fragment). ***The aim*** *is to study the quantum-chemical parameters of the listed groups of the compounds in order to predict possible ways of their interaction with the most aggressive and dangerous of the active oxygen species (ROS) – a hydroxyl radical.* ***Materials and methods****. For the analyzed structures, the Mulliken charges (a.u.), bond numbers (Nμ), unsaturation index (IUA), and electron density values on all 9-carbon atoms of the cinnamoyl fragment have been determined. The calculations have been carried out on a workstation with an Intel Xeon E5-1620 3.5 GHz processor, 20 GB of RAM. The semi-empirical method PM7 was used (WinMopac 2016 program). The ORCA 4.1 program was used to calculate the energies of homolytic cleavage of the O – H bond.* ***Results****. The analysis of Mulliken charges (a.u.), bonded numbers (Nμ), unsaturation indices (IUA), and electron density revealed a number of regularities on the basis of which it can be concluded, that taking into account the nature of the substituent, the most probable for addition in the aryl residueare positions C-1, C-2, C-3, C-4 and C-5. In the propenone fragment, the radical HO· first attacks position 8, then 7. For the hydroxy-substituted, the energy of the homolytic breaking of the H – O bond has been determined and it has been established that the spatial difficulty of phenols (compounds 13k, 13x, 13f, 14k, 14x, 14f) H-O bonds are the smallest and on average are -160.63 kJ/mol. It has also been established that the higher the positive Mulliken charge on the carbon atom with which the phenolic hydroxyl is bound, the lower the energy of the homolytic breaking of the H – O bond and the more stable the resulting phenoxy radicalis.* ***Conclusion.*** *The carried out quantum chemical calculations allow us to conclude that the studied classes of compounds can be used to bind the hydroxyl radical formed in the body, causing various kinds of mutations, leading, among other things, to the development of oncological diseases.*

Keywords: *hydroxyl radical, cinnamic acid derivatives, chalcones, flavanones, Mulliken charges, bond numbers, unsaturation index, electron density*

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ИСПОЛЬЗОВАНИЕ КВАНТОВО-ХИМИЧЕСКИХ ПАРАМЕТРОВ ДЛЯ ПРОГНОЗИРОВАНИЯ АНТИРАДИКАЛЬНОЙ (НО·) АКТИВНОСТИ РОДСТВЕННЫХ СТРУКТУР, СОДЕРЖАЩИХ ЦИННАМОИЛЬНЫЙ ФРАГМЕНТ. I. ПРОИЗВОДНЫЕ КОРИЧНОЙ КИСЛОТЫ, ХАЛКОНА И ФЛАВАНОНА

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Изучено 45 соединений, объединяющих 3 группы производных коричной кислоты, халкона и флаванона, каждая из которых включает по 15 веществ. Анализируемые соединения содержат общий структурный фрагмент, представляющий собой остаток коричной кислоты (циннамоильный фрагмент). ***Цель работы –*** *изучение квантово-химических параметров перечисленных групп соединений с целью прогнозирования возможных путей их взаимодействия с наиболее агрессивным и опасным из числа активных форм кислорода (АФК) гидроксильным радикалом.* ***Материалы и методы.*** *Для анализируемых структур определены Малликеновские заряды (а.е.), связевые числа (Nμ), индекс ненасыщенности (IUA) и величины электронной плотности на всех 9-атомах углерода циннамоильного фрагмента. Расчеты осуществлены на рабочей станции с процессором IntelXeonE5-1620 3,5 ГГц, 20 Гб оперативной памяти. При этом использован полуэмпирический метод PM7 (программа WinMopac 2016). Для расчетов энергий гомолитического расщепления связи О–Н использована программа ORCA 4.1.* ***Результаты.*** *Анализ величин Малликеновских зарядов (а.е.), связевых чисел (Nμ), индексов ненасыщенности (IUA) и электронной плотности позволил выявить ряд закономерностей, на основании которых можно делать выводы о том, что с учетом природы заместителей наиболее вероятными для присоединения в арильном остатке являются положения С-1, С-2, С-3, С-4 и С-5. В пропеноновом фрагменте радикал НО* в первую очередь атакует положение 8, затем 7. Для гидроксизамещенных определена энергия гомолитического разрыва связи Н-О и установлено, что у пространственно затрудненных фенолов (соединения 13к, 13х, 13ф, 14к, 14х, 14ф) энергия разрыва связи Н-О наименьшая и в среднем составляет – 160,63 кДж/моль. Установлено также, что,чем выше положительный Малликеновский заряд на атоме углерода, с которым связан фенольный гидроксил, тем ниже энергия гомолитического разрыва связи Н-О и тем более устойчив образующийся феноксильный радикал.* ***Заключение.*** *Проведенные квантово-химические расчеты позволяют сделать вывод о том, что изучаемые классы соединений могут быть использованы для связывания образующегося в организме гидроксильного радикала, вызывающего различного рода мутации, приводящие, в том числе, к развитию онкологических заболеваний.*

Ключевые слова: *гидроксильный радикал, производные коричной кислоты, халконы, флаваноны, Малликеновские заряды, связевые числа, индекс ненасыщенности, электронная плотность*

INTRODUCTION

Currently, experimental biochemistry and clinical pharmacology have accumulated extensive material indicating the relationship of free radical oxidation processes involving reactive oxygen species (ROS) and many diseases. It is known that in violation of the mechanisms of antioxidant protection in the body there is an accumulation of ROS, of which the HO-radical is the most dangerous. It is able to interact with the nitrogenous bases of DNA and RNA, which contributes to the formation of various types of mutations [1, 2]. It also interacts with phospholipids of cell membranes, increasing the level of their peroxidation and resulting in reperfusion tissue damage, carcinogenesis and other pathological processes [2, 3].

In case of disturbances in the equilibrium processes involving ROS, natural compounds — derivatives of cinnamic acid, chalcones and flavanones, containing a common cinnamoyl fragment, are getting more and more become important. In flavonoids it is the main conjugate chain and, in essence, it represents the residue of cinnamic acid. These three groups of compounds are interconnected by biogenetic transformations [4–6].

The listed representatives of polyphenolic compounds are characterized by a broad spectrum of pharmacological activity, which is probably due to their high antiradical activity.

THE AIM istostudy the quantum-chemical characteristics of cinnamic acid derivatives, chalcones and flavanones containing substituents in the aryl moiety conjugation of the main chain to predict their possible interactions with the hydroxyl radical HO.

MATERIALS AND METHODS

The objects of the study were hydroxy and methoxy substituted cinnamic acid, chalcone and flavanone derivatives in the aryl residue of the cinnamoyl moiety, 45 compounds in total. Quantum-chemical parameters of the analyzed structures were calculated on a workstation with an Intel Xeon E5-1620 3.5 GHz processor, 20 GB of RAM.

The hydroxyl radical HO, whose life expectancy in a biological medium is about 10^{-9} seconds, represents the greatest danger among the active oxygen species (ROS).

One of the ways of formation of a hydroxyl radical in the body can be the Fenton reaction or the oxidation of Fe^{2+} to the Fe^{3+} hypochlorite anion, which, in turn, is formed in phagocytes.

It has been proved that the yield of hydroxyl radical OH· in the second case is higher than in the Fenton reaction [8].

The same radical can be formed by the reaction of Haber-Weiss [8].

The consequences of these reactions involving bivalent iron are obvious: the “extraction” of Fe^{2+} cation from the systems containing it and its subsequent oxidation to Fe^{3+}, which is extremely dangerous in itself, since it contributes to the destruction of blood heme and iron-containing endogenous substances.

On the other hand, the hydroxyl radical, interacting with the amino acid fragments of proteins, causes denaturation of the latter and subsequent inactivation of enzymes.

There is an opinion that the OH· radical·is able to selectively accumulate near the DNA [9].

Possessing sufficiently high electrophilic properties, it can not only hydroxylate the nitrogenous bases of nucleic acids, but also contribute to the subsequent breaking of both carbohydrate bridges between nucleotides and hydrogen bonds of “interlaced” polynucleotide chains [2]. It is clear that further processes will mutate or damage genes.

In the lipid layer of cell membranes, the HO· initiates a chain reaction of lipid oxidation by a radical mechanism, which leads to cell damage and cell death.

Biochemical processes involving ROS in the physiological norm are controlled by both enzyme and non-enzyme components of cells. In case of disturbances in the equilibrium processes involving ROS, natural antioxidants, such as polyphenolic compounds as cinnamic acid derivatives, as well as flavonoids (chalcones, flavanones, flavones and flavonols), become important.

Due to the structural diversity, as well as the totality of the manifested pharmacological effects, they occupy a special place among natural antioxidants.

It is known that cinnamic acid is directly involved in the biosynthesis of flavonoids [4]. Comparing the structures of cinnamic acid and flavonoids, it is easy to verify that the common structural fragment in all the compounds is the cinnamoyl fragment, which is essentially a cinnamic acid residue (Fig. 1).

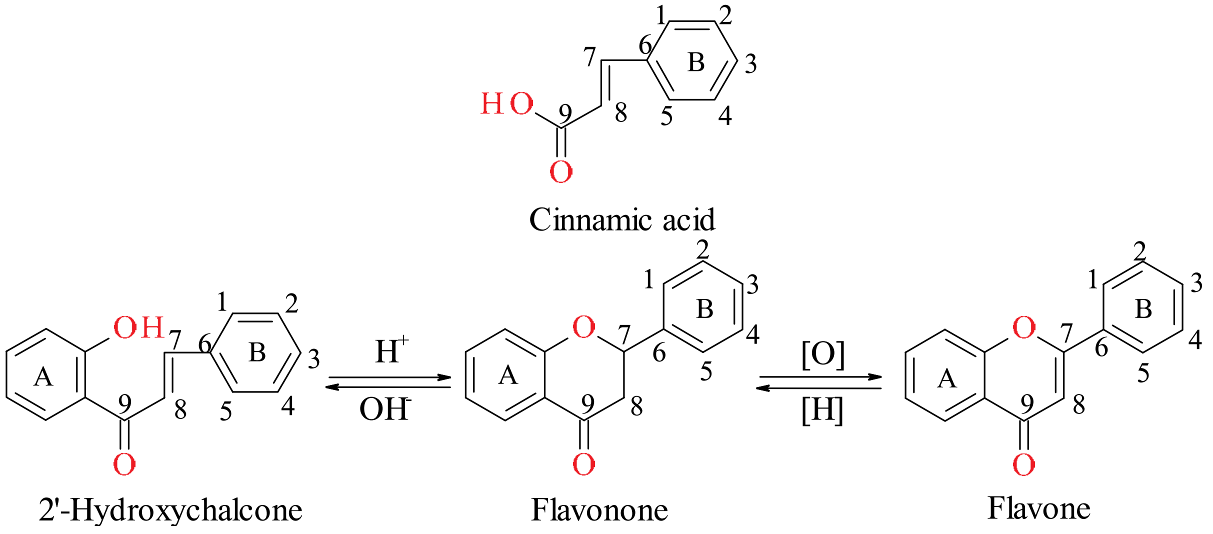


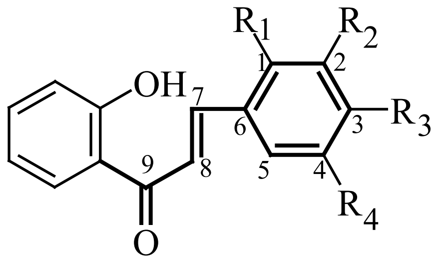
Figure. 1. Structural features of chalcone, flavanone and flavone

It should be noted that with slight changes in the pH-environment, the chalcones become flavanones and vice versa: flavanone prevails in the acidic environment, and chalcone prevails in the alkaline one. This circumstance is important from the point of view of the biological activity of chalcones and flavanones.

It is clear from the presented structures, that the main conjugation chain is formed thanks to the cynnamoyl fragment, and the transfer of electronic effects exerted by substituents in ring B, occurs through this chain.

In continuation of our earlier studies [10–13], and also taking into account the structural proximity of cinnamon acids, chalcones and flavanones (the presence of a cinnamoyl fragment), we found it advisable to a priori examine the activity of the chalcones and flavanones in relation to the hydroxyl radical OH· using such quantum-chemical parameters as Mulliken charges (a.u.), bond numbers (Nμ), theoretical valence (Vμ), unsaturation index (IUA), and electron density. Table 1 presents the analyzed compounds, which are designated respectively 1k–15k (derivatives of cinnamic acid), 1x–15x (derivatives of chalcone), 1f–15f (derivatives of flavanone).

Table 1. Derivatives of cinnamic acid (k), chalcone (x) * and flavanone with substituents in the aromatic core of the main conjugation chain



No.			Position of substituents			
K	x*	f	1	2	3	4
1k	1x	1f	H	H	H	H
2k	2x	2f	OH	H	H	H
3k	3x	3f	CH_3O	H	H	H
4k	4x	4f	H	OH	H	H
5k	5x	5f	H	CH_3O	H	H
6k	6x	6f	H	H	OH	H
7k	7x	7f	H	H	CH_3O	H
8k	8x	8f	H	OH	OH	H
9k	9x	9f	H	CH_3O	OH	H
10k	10x	10f	H	OH	CH_3O	H
11k	11x	11f	H	CH_3O	CH_3O	H
12k	12x	12f	H	OH	OH	OH
13k	13x	13f	H	CH_3O	OH	CH_3O
14k	14x	14f	H	$C(CH_3)_3$	OH	$C(CH_3)_3$
15k	15x	15f	H	CH_3O	CH_3O	CH_3O

** Note: chalcone derivatives containing an OH group in the ortho-position to the carbonyl are considered, since in its absence the chalcone-flavanone transition is impossible*

Previously, using semi-empirical quantum-chemical methods, we studied the reactivity indices of cinnamic acid derivatives with respect to the hydroxyl radical [10]. This made it possible to identify the most reactive centers in the cinnamoyl fragment: the interaction of cinnamic acid with the OH-radical electrophilic in properties occurs primarily at the C-8 position, since this atom is characterized by the lowest degree of "saturation" (the lowest bond number), the highest electron density, and the greatest negative charge compared to its two nearest atoms. Further interaction of cinnamic acid with the formation of the corresponding adducts is possible according to the C-7, C-6, C-1 and C-5 positions[1].

Taking into account the trends revealed in cinnamic acid, we considered it expedient to determine the most probable centers of primary attack by the OH· radical of chalcone and flavanone.

The quantum chemical characteristics listed above were calculated using the PM7 semi-empirical method (WinMopac 2016 program) for chalcones and flavanones containing hydroxy and methoxy groups in the aryl moiety of the main conjugation chain.

Tables 2, 3, 4 present the distribution of Mulliken charges (a.u.), bond numbers (Nμ), unsaturation index (IUA) and electron density on the carbon atoms of the cinnamoyl fragment of the two derivatives of cinnamic acid (6k and 7k), chalcone (6x and 7x) and flavanone (6f and 7f).

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[1] Henceforward, numbering of atoms in the analyzed structures is given not in accordance with the IUPAC rules, but in accordance with the calculation programs. For cinnamic acid, the carbon numbering generated by the programs is shown. To make it easier and more convenient to compare the results obtained, authors have kept this numbering for chalcones and flavanones.

Table 2. Values of Mulliken charges (a.u.), bond numbers (Nµ), unsaturation index (IUA) and electron density on the carbon atoms of the cinnamoyl fragment of compounds 6k and 7k, 6x and 7x, 6f and 7f

	1		2		3		4		5		6		7		8	
	6k	7k	6k	7k	6k	7k	6k	7k	6k	7k	6k	7k	6k	7k	6k	7k
a.u.	-0.044	-0.043	-0.262	-0.269	0.317	0.217	-0.326	-0.317	-0.042	-0.046	-0.134	-0.138	0.002	0.008	-0.316	-0.321
Nµ	3.810	3.813	3.789	3.782	3.774	3.774	3.777	3.774	3.811	3.810	3.836	3.832	3.866	3.864	3.790	3.787
IUA	0.154	0.151	0.167	0.174	0.132	0.149	0.173	0.176	0.154	0.156	0.148	0.150	0.079	0.080	0.157	0.158
el.d.	4.044	4.043	4.262	4.270	3.683	3.722	4.326	4.317	4.042	4.046	4.134	4.134	3.997	3.991	4.316	4.321
	6x	7x	6x	7x	6x	7x	6x	7x	6x	7x	6x	7x	6x	7x	6x	7x
a.u.	-0.047	-0.046	-0.265	-0.272	0.317	0.277	-0.322	-0.314	-0.044	-0.047	-0.134	-0.138	0.009	0.016	-0.337	-0.342
Nµ	3.810	3.814	3.788	3.783	3.773	3.775	3.777	3.774	3.809	3.810	3.836	3.835	3.851	3.849	3.805	3.803
IUA	0.156	0.152	0.169	0.173	0.133	0.148	0.173	0.177	0.156	0.156	0.147	0.148	0.091	0.091	0.147	0.147
el.d.	4.047	4.046	4.265	4.272	3.683	3.722	4.322	4.314	4.044	4.047	4.134	3.983	3.990	3.983	4.337	4.342
	6f	7f	6f	7f	6f	7f	6f	7f	6f	7f	6f	7f	6f	7f	6f	7f
a.u.	-0.068	-0.069	-0.248	-0.253	0.306	0.265	-0.316	-0.305	-0.050	-0.057	-0.161	-0.162	0.138	0.141	-0.441	-0.440
Nµ	3.826	3.222	3.786	3.780	3.783	3.785	3.777	3.774	3.826	3.826	3.821	3.819	3.838	3.839	3.818	3.820
IUA	0.140	0.139	0.172	0.179	0.126	0.142	0.175	0.179	0.139	0.140	0.160	0.162	0.064	0.162	0.115	0.114
el.d.	4.068	4.070	4.248	4.253	3.693	3.735	4.316	4.305	4.050	4.057	4.161	4.162	3.861	3.859	4.441	4.440

Table 3. Values of Mulliken charges (a.u.) of bond numbers (Nμ), index unsaturation (IUA) and the electron density on the carbon atoms of cinnamoyl moiety 8k and 9k compounds 8h and 9h, 8f and 9F

	1		2		3		4		5		6		7		8	
	8k	9k	8k	9k	8k	9k	8k	9k	8k	9k	8k	9k	8k	9k	8k	9k
a.u.	-0.105	0.105	-0.216	-0.217	0.229	0.225	0.126	0.094	-0.212	-0.206	-0.060	-0.066	-0.008	-0.004	-0.303	-0.306
Nμ	3.803	3.802	3.786	3.788	3.763	3.755	3.761	3.766	3.767	3.762	3.839	3.839	3.868	3.867	3.794	3.792
IUA	0.168	0.169	0.176	0.174	0.172	0.178	0.172	0.183	0.203	0.207	0.152	0.152	0.08	0.08	0.156	0.156
el.d.	4.105	4.105	4.216	4.218	3.770	3.775	3.873	3.905	4.212	4.206	4.060	4.066	4.008	4.004	4.303	4.306
	8x	9x	8x	9x	8x	9x	8x	9x	8x	9x	8x	9x	8x	9x	8x	9x
a.u.	-0.110	-0.109	-0.218	-0.225	0.228	0.192	0.129	0.141	-0.213	-0.280	-0.059	0.061	-0.02	0.004	-0.324	-0.328
Nμ	3.804	3.806	3.788	3.780	3.763	3.760	3.761	3.760	3.766	3.763	3.841	3.838	3.854	3.853	3.809	3.807
IUA	0.169	0.166	0.175	0.183	0.172	0.189	0.172	0.175	0.203	0.206	0.151	0.153	0.090	0.090	0.147	0.147
el.d.	4.110	4.109	4.218	4.225	3.771	3.807	3.870	3.858	4.214	4.220	4.059	4.061	4.022	3.996	4.324	4.328
	8f	9f	8f	9f	8f	9f	8f	9f	8f	9f	8f	9f	8f	9f	8f	9f
a.u.	-0.196	-0.198	0.206	0.165	0.147	0.163	-0.232	-0.242	-0.137	-0.134	-0.073	-0.080	0.130	0.133	-0.437	-0.435
Nμ	3.765	3.760	3.777	3.776	3.748	3.746	3.799	3.797	3.815	3.815	3.833	3.833	3.840	3.841	3.818	3.820
IUA	0.197	0.205	0.162	0.178	0.183	0.187	0.169	0.170	0.156	0.156	0.159	0.158	0.064	0.062	0.115	0.114
el.d.	4.196	4.198	3.793	3.835	3.852	3.837	4.232	4.242	4.137	4.134	4.073	4.080	3.869	3.866	4.437	4.435

Table 4. Values of Mulliken charges (a.u.) of bond numbers (Nμ), unsaturation index (IUA) and the electron density on the carbon atoms cinnamoyl moiety 10k and 13K compounds, 10x and 13x, 10f and 13f

	1		2		3		4		5		6		7		8	
	10k	13k	10k	13k	10k	13k	10k	13k	10k	13k	10k	13k	10k	13k	10k	13k
a.u.	-0.105	-0.271	-0.223	0.183	0.193	0.102	0.138	0.146	-0.218	-0.268	-0.063	0.008	-0.002	-0.01	-0.308	-0.298
Nμ	3.806	3.728	3.779	3.776	3.760	3.712	3.760	3.763	3.765	3.738	3.837	3.845	3.866	3.867	3.792	3.797
IUA	0.165	0.228	0.184	0.179	0.189	0.234	0.175	0.186	0.205	0.219	0.154	0.149	0.081	0.08	0.156	0.154
el.d.	4.105	4.271	4.223	3.817	3.806	3.897	3.861	3.854	4.218	4.268	4.063	3.991	4.002	4.001	4.308	4.298
	10x	13x	10x	13x	10x	13x	10x	13x	10x	13x	10x	13x	10x	13x	10x	13x
a.u.	-0.109	-0.242	-0.220	0.203	0.224	0.057	0.097	0.171	-0.206	-0.290	-0.066	0.023	0.002	-0.025	-0.327	-0.303
Nμ	3.802	3.733	3.788	3.774	3.755	3.699	3.766	3.770	3.761	3.734	3.840	3.852	3.853	3.852	3.807	3.811
IUA	0.170	0.224	0.174	0.176	0.179	0.235	0.183	0.176	0.208	0.217	0.152	0.142	0.09	0.142	0.147	0.150
el.d.	4.109	4.242	4.220	3.796	3.776	3.943	3.902	3.830	4.206	4.290	4.066	3.976	3.998	3.976	4.327	4.303
	10f	13f	10f	13f	10f	13f	10f	13f	10f	13f	10f	13f	10f	13f	10f	13f
a.u.	-0.194	-0.265	0.200	0.220	0.114	0.05	-0.224	0.176	-0.140	-0.292	-0.076	-0.004	0.132	0.129	-0.438	-0.430
Nμ	3.766	3.746	3.771	3.771	3.752	3.705	3.795	3.765	3.815	3.745	3.832	3.835	3.841	3.838	3.819	3.818
IUA	0.196	0.205	0.167	0.176	0.196	0.227	0.173	0.180	0.157	0.203	0.159	0.157	0.062	0.063	0.114	0.116
el.d.	4.194	4.260	3.800	3.779	3.885	3.949	4.224	3.823	4.140	4.293	4.076	4.004	3.867	3.870	4.438	4.430

It is characteristic for the C-7 and C-8 atoms to have the same dynamics of changes in parameters as it had been in cinnamic acid. In the analyzed structures, the carbon atom C-9 is characterized by a significantly lower electron density and a higher positive Mulliken charge, although the bond number is insignificant (third decimal place), it is higher than those for C-8 and C-7. The highest negative Mulliken charge and the electron density, as well as the smallest bond numbers compared to the two nearest atoms, are concentrated on the C-8 atom of all the three types of the structures under consideration. Similar electronic effects are easy to explain, if we take into consideration the fact that with respect to the propenone moiety, the electron-donating hydroxy and methoxy groups at positions 1 and 3 (ortho and para positions with respect to the propene unit) contribute to the enhancement of the polar conjugation and, consequently, to an increase in the Mulliken charge and electron density on C-8 (compounds 2, 3, 6, 7) compared with the parent structure of each group of the analyzed compounds.

If the hydroxy- and methoxy groups are in position 2 of the aryl fragment (compounds 4 and 5), then the electron density and Mulliken charge decrease, but the same parameters increase on the C-1, C-3 and C-5 atoms, that is, in two ortho- (P-1 and P-3) and para-positions (P-5) (table 5). This dependence is repeated in all the three types of the structures under consideration - 4k, 4x, 4f and 5k, 5x and 5f. Such electronic effects are in good agreement with the contribution of the Taft constants [14].

Table 5. Values of Mulliken charges (a.u.), electron density and bond numbers (Nμ) on carbon atoms in o- and p- positions with respect to the substituent for the derivatives of cinnamic acid, chalcone and flavanone, numbered 2, 3 and 4

	Unsubstitute dcinnamic acid			Unsubstitute dchalcone			Unsubstituted flavanone		
Cv	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ
1	-0.118	4.1180	3.812	-0.122	4.122	3.813	-0.141	4.141	3.827
2	-0.159	4.1590	3.852	-0.161	4.162	3.852	-0.145	4.145	3.849
3	-0.125	4.1249	3.836	-0.121	4.126	3.837	-0.135	4.135	3.845
4	-0.159	4.1595	3.854	-0.156	4.156	3.854	-0.151	4.151	3.852
5	-0.126	4.1260	3.816	-0.128	4.128	3.814	-0.132	4.133	3.829
6	-0.054	4.0540	3.858	-0.053	4.054	3.856	-0.081	4.081	3.840
7	-0.020	4.0200	3.869	-0.013	4.013	3.855	0.122	3.877	3.840
8	-0.298	4.9810	3.798	-0.319	4.319	3.814	-0.440	4.440	3.819

	2k			2x			2f		
Cv	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ
8	-0.288	4.288	3.798	-0.364	4.364	3.763	-0.446	4.442	3.812
2	-0.234	4.047	3.852	-0.268	4.268	3.787	-0.229	4.229	3.803
4	-0.149	4.062	3.854	-0.238	4.238	3.842	-0.197	4.197	3.844
1	-0.046	4.322	3.832	0.342	3.658	3.747	0.284	3.715	3.777

	3k			3x			3f		
Cv	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ
8	-0.301	4.301	3.781	-0.368	4.368	3.785	-0.439	4.439	3.819
2	-0.238	4.050	3.838	-0.270	4.270	3.780	-0.309	4.310	3.773
4	-0.161	4.060	3.783	-0.235	4.235	3.842	-0.227	4.228	3.834
1	-0.050	4.314	3.833	0.309	3.690	3.740	0.269	3.730	3.777

	4k			4x			4f		
Cv	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ
8	-0.283	4.283	3.804	-0.299	4.299	3.819	-0.437	4.437	3.818
1	-0.290	4.290	3.740	-0.230	4.230	3.750	-0.240	4.240	3.747
3	-0.228	4.228	3.779	-0.296	4.296	3.769	-0.303	4.303	3.774
5	-0.205	4.205	3.800	-0.210	4.210	3.803	-0.223	4.223	3.813

	5k			5x			5f		
Cv	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ	a.u.	el.d.	Nμ
8	-0.290	4.290	3.802	-0.303	4.303	3.819	-0.436	4.436	3.818
1	-0.278	4.278	3.737	-0.234	4.234	3.743	-0.252	4.252	3.757
3	-0.233	4.233	3.773	-0.285	4.285	3.766	-0.293	4.293	3.770
5	-0.204	4.204	3.798	-0.210	4.210	3.803	-0.215	4.210	3.814

Note: k – cinnamic acid, x – chalcone, f – flavanone

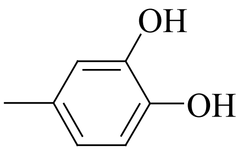
Thus, the primary hydroxyl radical electrophilic attack will take place primarily at position C-8, and then at the C-7 position.

A similar conclusion is valid for the considered types of the analyzed compounds, as shown before [11, 12].

Using a similar approach to interpret the possible attack paths of the monosubstituted derivatives by the OH-radical (compounds 2k, 2x, 2f – 7k, 7x, 7f) taking into account the quantum chemical parameters, it can be assumed that the most likely are the C-2 and C-4 positions for compounds 2 and 3, since they are characterized by the highest IUA values. If the substituent is in position 2, then the attack is likely to occur in C-1, C-3 or C-5 positions of the phenyl fragment of all three types of structures under consideration due to high IUA values. For compounds of types 6 and 7, the attack of a hydroxyl radical is equally probable in the C-2 and C-4 positions for the same reasons as mentioned above (Tables 2, 3, 4, 5).

In the case of disubstituted for the aryl fragment, the dynamics of changes in the Mulliken charges, the unsaturation index and the electron density in compounds 8, 9 and 10 of all the three types of the structures under consideration practically coincide and actually make the same electronic contribution to the C-8 propene unit.

It should be emphasized that two hydroxy- or hydroxy- and methoxy-groups in positions 2 and 3 of the aryl fragment have a competitive effect on the conjugation system: the effect of the para-substituent is partially extinguished by the inconsistent influence of the same substituent in position 2. This conclusion can be illustrated by Taft σ-constants for –OH and –OCH3 groups [14]:

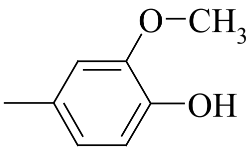


σ = 0.127

σ = -0.370

∑=-0.243

Compounds 8k, 8x, 8f

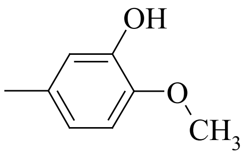


σ = 0.115

Σ= -0.370

∑=-0.255

Compounds 9k, 9x, 9f



σ = 0.127

σ= -0.268

∑= -0.141

Compounds 10k, 10x, 10f

When interpreting antiradical (HO·)activity of polyhydroxy cinnamic acid derivatives, chalcones and flavanones, one should take into account their ability to bind reactive oxygen species not only with the participation of carbon atoms of the aryl radical, but also due to the homolytic breaking of the H – O bond of the phenolic hydroxy-group to form an intermediate adduct — the phenoxyl radical.

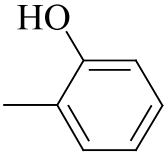
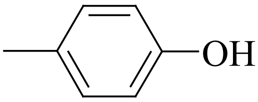
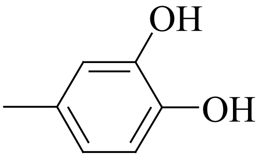
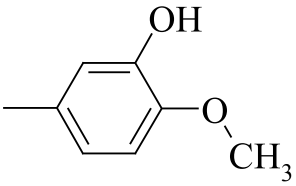
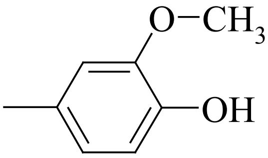
Earlier, when analyzing the antiradical activity of polyhydroxychalcons, we calculated the energies of homolytic breaking of H–O bonds in monohydroxy-compounds in which the hydroxy-group is located at C-3 or C-4, as well as for disubstituted ones, as shown below.

In continuation of these studies using the ab initio method, we calculated the energies of the homolytic breaking of the H O bond with the transition of the hydrogen atom to the hydroxyl radical in the cinnamoyl disubstituted along the aryl residue. The relationship between the breaking energy of the H–O bond and the unsaturation index (IUA) of the carbon atom which the substituent is associated has been revealed. For this program, ORCA 4.1 was used. The optimization of the geometry of molecules was performed using the density functional theory (UB3LYP) method using the set of basis functions 3-21G*. Vibrational analysis, as well as the calculation of thermodynamic functions (enthalpy, entropy, and Gibbs energy) were performed on the basis of the density functional theory (UB3LYP) using the set of basic functions 6-311G** [15, 16]. It has been established that the lower the bond breaking energy, the higher the IUA value is (Table 6).

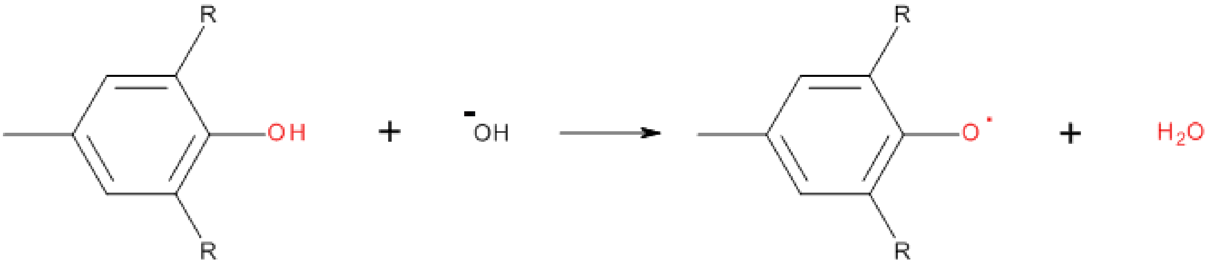
In the presented data, a clear relationship can be traced: the larger the unsaturation index (IUA) of the aryl carbon atom with which the hydroxy group is associated, the lower the energy of the H – O homolytic bond break is. There is a similar relationship for bond numbers (Table 3).

In the list of the compounds subjected to quantum-chemical study, we have considered three types of compounds containing three substituents in positions 2, 3, 4 of the aryl fragment and designated by numbers 12, 13 and 14.

Table 6. Gibbs free energy of homolytic breaking of the H–O bond

Structuralfragment	Breaking energy of the O – H bond	IUA (C-1)	IUA (C-2)	IUA (C-3)
	-150.30	0.135 (2k)	-	-
		0.152 (2x)	-	-
		0.145 (2f)	-	-
	-137 , 70	-	-	0.132 (6k)
		-	-	0.133 (6x)
		-	-	0.126 (6f)
	-173.89	-	0.175 (8k)	0.172 (8k)
		-	0.173 (8x)	0.172 (8x)
		-	0.162 (8f)	0.183 (8f)
	-130.01	-	0.184 (10k)	0.189 (10k)
		-	0.174 (10x)	0.179 (10x)
		-	0.167 (10f)	0.196 (10f)
	-174.26	-	0.174 (9k)	0.178 (9k)
		-	0.183 (9x)	0.189 (9x)
		-	0.178 (9f)	0.187 (9f)

For these compounds, the energies of the homolytic O – H bond have been calculated resulting in corresponding phenoxyl radical in position C-3 and the addition of a hydrogen atom to a hydroxyl radical. In our opinion, it can be represented by the following scheme:



This reaction was simulated by the molecular dynamics method in a 3-21G* force field using the density functional theory (UB3LYP) method for 50 picoseconds. In the process of simulation, a hydroxyl radical attacks a phenolic hydroxyl group, bonding a hydrogen atom with its oxygen. In the course of the oscillation of the phenolic hydroxyl group, covalent bonding of the hydrogen atom of the phenol hydroxide to the oxygen atom of the hydroxyl radical occurs. After that, a free water molecule and a phenol radical are formed. Figure 2 shows a graph of the dependence of potential energy of the simulated system on time.

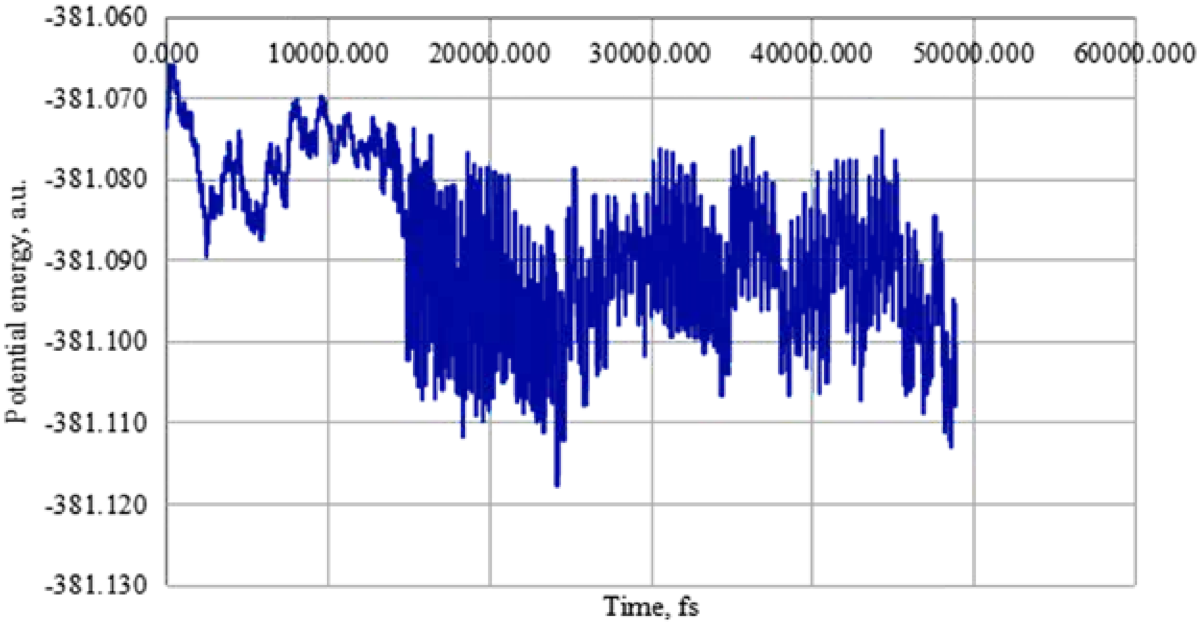
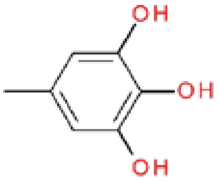
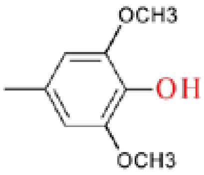
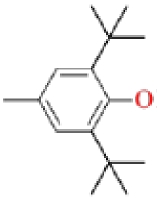


Figure 2. Dynamics of potential energy changes in the process of simulating homolytic cleavage of the OH bond of the phenolic hydroxyl

According to the results of the molecular dynamics simulation, the activation energy of a simulated reaction of the homolytic cleavage of phenolic hydroxyl with the transition of a hydrogen atom to a hydroxyl radical has been determined. The activation energy was 34.918 kJ/mol, which indicates that the reaction proceeds fairly quickly at a human body temperature (310 K).

It should be notified that this phenolic hydroxyl is surrounded by two ortho substituents, which have a shielding effect. The phenoxyl radical formed by the C-3 hydroxyl in structures 12, 13, and 14 belongs to the spatially obstructed types of radicals and is therefore more stable.

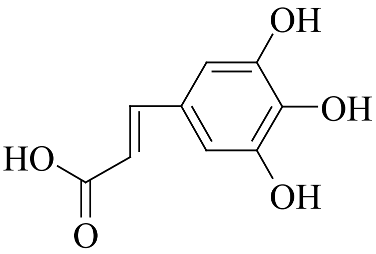
Table 7. Gibbs free energy of homolytic breaking of the H – O bond

Substance	Structuralfragment	Energy of O-Hsplittingbreaking
12x		-171.21
12k		-170.72
12f		-166.79
13x		-164.66
13k		-117.04
13f		-159.40
14x		-178.31
14k		-181.29
14f		-163.08

The same dependence as in the case of disubstituted ones, is observed here, i.e. the lower the energy of the homolytic breaking of the H – O bond in sterically hindered phenols, the higher the IUA values and the positive charge of the carbon atom, phenolic hydroxyl is bound with (in this case C-3). It should be notified that compound 14k (4-hydroxy-3,5-di-tertbutyl-cinnamic acid) was previously synthesized by us in accordance with the forecast [11], since its high activity had been predicted. An experimental study of the pharmacological properties confirmed our prediction: the substance is characterized by cerebroprotective [17], antioxidant [18], endothelioprotective [19] and actoprotective [20] types of activity.

It is possible to predict with high probability the same level of activity for compounds 14x and 14f, since their quantum-chemical characteristics are almost identical with compound 14k.

With regard to the analysis of structures of all three types, we found it expedient to take into account the molar mass in the characterization of bonded numbers (Nμ), unsaturation index (IUA), and electron density. For this purpose, the total value of the listed characteristics was determined for each compound, which was then referred to the molar mass. The partial dividing of the total valuesof Nμ, IUA and electron density by the molar mass, in our opinion, characterizes the specific value of the listed parameters in terms of the mass unit of the molecule. In our opinion, a similar indicator in the future may be useful for the interpretation of biologically active related compounds. The results are presented below:

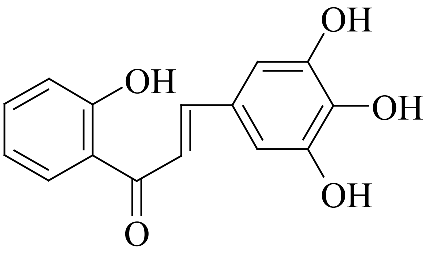


$C_9H_8O_5$ M=196

$$\frac{\sum_{N_\mu}}{M} = \frac{33.99}{196} = 0.1734$$

$$\frac{\sum_{IUA}}{M} = \frac{1.41}{196} = 0.0072$$

$$\frac{\sum_{el.d.}}{M} = \frac{35.685}{196} = 0.1820$$

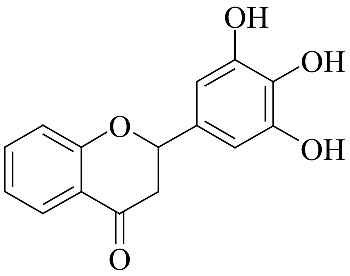


$C_{15}H_{12}O_5$ M=272

$$\frac{\sum_{N_\mu}}{M} = \frac{34.04}{272} = 0.1251$$

$$\frac{\sum_{IUA}}{M} = \frac{1.41}{272} = 0.0051$$

$$\frac{\sum_{el.d.}}{M} = \frac{35.874}{272} = 0.1319$$

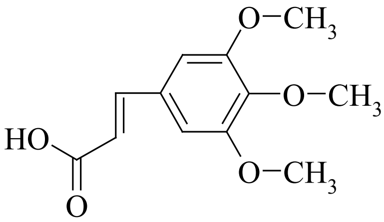


$C_{15}H_{12}O_5$ M=272

$$\frac{\sum_{N_\mu}}{M} = \frac{34}{272} = 0.1259$$

$$\frac{\sum_{IUA}}{M} = \frac{1.42}{272} = 0.0052$$

$$\frac{\sum_{el.d.}}{M} = \frac{35.205}{272} = 0.1294$$

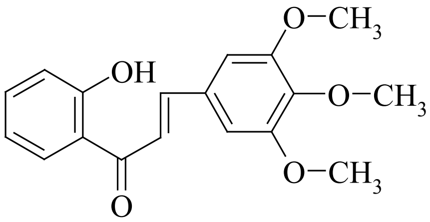


$C_{11}H_{12}O_5$ M=224

$$\frac{\sum_{N_\mu}}{M} = \frac{33.94}{224} = 0.1515$$

$$\frac{\sum_{IUA}}{M} = \frac{1.49}{224} = 0.0066$$

$$\frac{\sum_{el.d.}}{M} = \frac{35.798}{224} = 0.1598$$

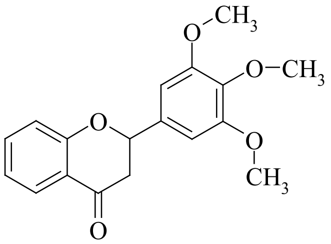


$C_{15}H_{16}O_5$ M=276

$$\frac{\sum_{N_\mu}}{M} = \frac{34}{276} = 0.1231$$

$$\frac{\sum_{IUA}}{M} = \frac{1.49}{276} = 0.0054$$

$$\frac{\sum_{el.d.}}{M} = \frac{35.974}{276} = 0.1303$$

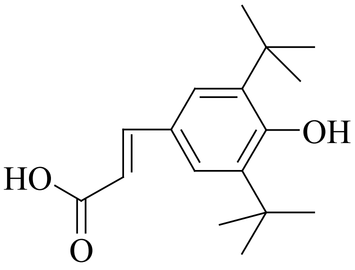


$C_{15}H_{16}O_5$ M=276

$$\frac{\sum_{N_\mu}}{M} = \frac{33.95}{276} = 0.1230$$

$$\frac{\sum_{IUA}}{M} = \frac{1.51}{276} = 0.0054$$

$$\frac{\sum_{el.d.}}{M} = \frac{35.906}{276} = 0.1301$$

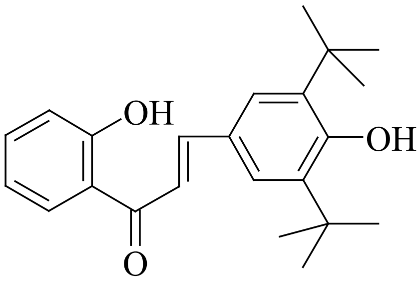


$C_{17}H_{24}O_3$ M=276

$$\frac{\sum_{N_\mu}}{M} = \frac{34.12}{276} = 0.1236$$

$$\frac{\sum_{IUA}}{M} = \frac{1.32}{276} = 0.0047$$

$$\frac{\sum_{el.d.}}{M} = \frac{35.974}{276} = 0.1303$$

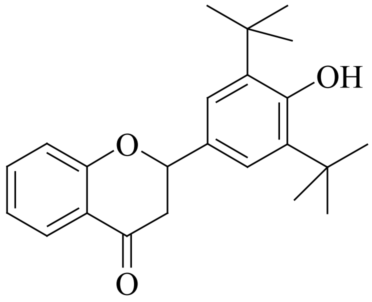


$C_{23}H_{28}O_3$ M=352

$$\frac{\sum_{N_\mu}}{M} = \frac{34.24}{352} = 0.0972$$

$$\frac{\sum_{IUA}}{M} = \frac{1.31}{352} = 0.0037$$

$$\frac{\sum_{el.d.}}{M} = \frac{36.204}{352} = 0.1028$$



$C_{23}H_{28}O_3$ M=352

$$\frac{\sum_{N_\mu}}{M} = \frac{34.13}{352} = 0.0970$$

$$\frac{\sum_{IUA}}{M} = \frac{1.36}{352} = 0.0386$$

$$\frac{\sum_{el.d.}}{M} = \frac{36.116}{352} = 0.1026$$

The attention of the scientistshas been attracted to very close values of specific indicators of bond numbers, indices of unsaturation and electron density for chalcone and flavanone. This fact once again confirms not only the ease of their interconversion, but, apparently, the same level of pharmacological properties.

CONCLUSION

Cinnamic acid differs from chalcone and flavanone in the absence of an aryl residue in its molecule, directly associated with carboxyl carbon, hence there are some differences in the values of quantum-chemical characteristics. But anyhow, all the three types of compounds can be successfully used to bind a hydroxyl radical in order to prevent those detrimental effects that the hydroxyl radical can cause, being, by Vladimirov Yu.A. metaphor, a destroyerradical, a killer radical.

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Conflict of interest

The authors declare no conflict of interest.

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