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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

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42 derivatives of 2’,4’-dihydroxychalcone, flavanone and flavone, containing the hydroxy group in position 7 (ring “A”), as well as substituents in the ring “B”, have been studied.

The aim is to study the quantum-chemical parameters of 2’,4’-dihydroxychalcone, flavanone and flavone derivatives containing a hydroxy group in position 7, in order to identify the effect of substituents on Mulliken charges (a.e) in the aromatic core “A”, bond numbers (Nµ), the unsaturation index (IUA) and the electron density of the carbon atoms of the cinnamoyl fragment.

Materials and methods. The listed above parameters 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 analysis of the values of quantum-chemical parameters, as well as their comparison with the corresponding indicators presented in Report I, revealed a number of important features associated with the influence of the hydroxy group in position 7 (ring “A”) on the studied quantum-chemical parameters of molecules. It has been established that the hydroxy group in the ring “A” does not significantly affect the Mulliken charge and the electron density of the carbon atoms of the propenone unit C-7→C-8→C-9. On atom C-9 (carbonyl carbon), the Mulliken charge always has a positive value, and the electron density is about 3.4670-3.4840 for all three groups of compounds. The transition from 2’,4’-dihydroxychalcone to flavanone and flavone by the formation of the pyrone heterocycle, is accompanied by an increase in the negative charge on C-8, which can be explained by the involvement of the oxygen heteroatom in the transmission of electronic effects. The hydroxy group in the ring “A”, has practically no effect on the charge and electron density of atoms. An analysis of the values of bond numbers and unsaturation indices suggests that atoms C-1 of 2’,4’-dihydroxychalcone and 7-hydroxyflavanone derivatives, are characterized by the lowest Nµ value; the lowest bond numbers are characteristic for atom C-8 derivatives of 7-hydroxyflavone. Consequently, the primary attack of the HO·radical will be directed at C-1 (in chalcones and flavanones) and at C-8 in flavones.

Conclusion. The performed quantum-chemical calculations make it possible to analyze the effect on the main quantum-chemical parameters of the molecule, which can be useful in predicting the biological activity of flavanoid compounds due to their antiradical effect on reactive oxygen intermediate species (ROIs).

Keywords: hydroxyl radical, chalcones, flavanones, flavones, 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.
II. ПРОИЗВОДНЫЕ 2',4'-ДИГИДРОКСИХАЛКОНА, А ТАКЖЕ ФЛАВАНОНА И ФЛАВОНА, СОДЕРЖАЩИЕ ГИДРОКСИГРУППУ В ПОЛОЖЕНИИ 7

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Изучено 42 производных 2',4-дигидроксихалкона, флаванона и флавона, содержащих гидроксигруппу в положении 7 (кольцо «А»), а также заместители в кольце «В».

Цель работы: изучение квантово-химических параметров производных 2',4'-дигидроксихалкона, флаванона и флавона, содержащих гидроксигруппу в положении 7, с целью выявления влияния заместителей в ароматическом ядре «А» на малликеновские заряды (а.е), связевые числа (Nµ), индекс ненасыщенности (IUA) и электронную плотность атомов углерода циннамоильного фрагмента.

Материалы и методы. Полуэмпирическим методом PM7 (программа WinMopac 2016) на рабочей станции с процессором IntelXeonE5-1620 3,5 ГГц, 20 Гб оперативной памяти рассчитаны перечисленные выше квантово-химические параметры анализируемых соединений.

Результаты и их обсуждение. Анализ величин квантово-химических параметров, а также их сравнение с соответствующими показателями, представленными в нашем сообщении I, позволил выявить ряд важных особенностей, связанных с влиянием гидроксигруппы в положении 7 (кольцо «А») на изучаемые параметры молекул. Установлено, что гидроксигруппа в кольце «А» не оказывает существенного влияния на малликеновский заряд и электронную плотность атомов углерода пропенонового звена С-7→С-8→С-9. На атоме С-9 (карбонильный углерод) малликеновский заряд всегда имеет положительное значение, а электронная плотность равна примерно 3,4670–3,4840 у всех трех групп соединений. Переход от 2',4'-дигидроксихалкона к флаванону и флавону путем формирования пиронового гетероцикла сопровождается повышением отрицательного заряда на С-8, что можно объяснить вовлечением гетероатома кислорода в процесс передачи электронных эффектов. Гидроксигруппа в кольце «А» практически не влияет на заряд и электронную плотность атомов. Анализ значений связевых чисел и индексов ненасыщенности свидетельствует о том, что наименьшим значением Nµ характеризуются атомы С-1 производных 2',4'-дигидроксихалкона и 7-гидроксифлаванона; наименьшие связевые числа характерны для атома С-8 производных 7-гидроксифлавона. Из этого следует, что первичная атака электрофильного по характеру радикала НО будет направлена на С-1 (у халконов и флаванонов) и С-8 у флавонов.

Заключение. Проведенные расчеты позволяют проанализировать влияние гидроксигруппы в кольце «А» на важнейшие квантово-химические параметры молекул, что может быть полезно при прогнозировании биологической активности флавоноидных соединений за счет их антирадикального влияния на активные формы кислорода (АФК).

Ключевые слова: гидроксильный радикал, халконы, флаваноны, флавоны, малликеновские заряды, связевые числа, индекс ненасыщенности, электронная плотность

INTRODUCTION

The known facts about the correlation of free radical oxidation with the formation of pathochemical processes and the resulting diseases, actualizes the problem of finding new biologically active compounds exhibiting antiradical properties [1-3]. In this regard, the structures containing three substituents in positions 2,3,4 of the aromatic nucleus of the main conjugation chain [4] (cinnamoyl fragment) – 2,3,4-trihydroxy-, 2,4-dimethoxy-3-hydroxy- and 2,4-di-*tert*-butyl-3-hydroxy derivatives – are of significant interest [5]. In this type of substitution, phenolic hydroxyl in C-3 is surrounded by two ortho substituents, due to the screening effect of which the spatially hindered phenoxy radical is characterized by a sufficient stability. It is important to notify that the Gibbs free energy of the homolytic cleavage of the **H**–**O** bond, is quite low and averages -163.61 kJ/mol. Modeling the molecular dynamics of changes in the potential **H**-O bond energy made it possible to determine the activation energy equal to 34.918 kJ/mol, and this indicates that this reaction is easy at the temperatures of ~ 36–37°C (~ 310 K).

Further on, 42 compounds – derivatives of chalcone, flavanone and flavone containing substituents in the ring “B” and a hydroxyl group in position 7 of the ring “A”, have been studied.

THE AIM is to study quantum-chemical parameters of the derivatives of 2’,4’-dihydroxychalcone, flavanone and flavone containing a hydroxy group in position 7 in order to identify the effect of substituents in the aromatic nucleus “A” on Mulliken charges (a.e), bond numbers (Nµ), unsaturation index (IUA) and the electron density of carbon atoms of the cinnamoyl fragment.

MATERIALS AND METHODS

The objects of the study were hydroxy and methoxy substituted, chalcone, flavone and flavanone derivatives in the aryl residue of the cinnamoyl fragment, 42 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.

RESULTS AND DISCUSSION

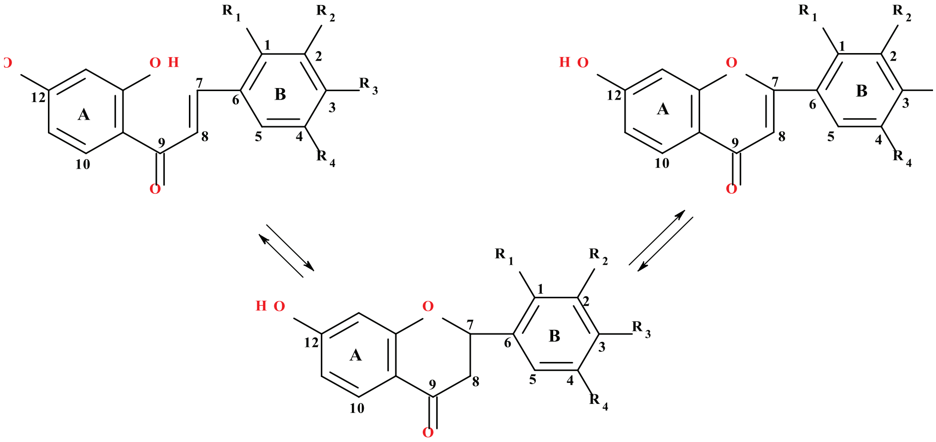
In this paper, the analyzed quantum-chemical parameters of compounds, their structures and symbols are presented in Table 1.

The Mulliken charges (a.e)

In our previous report [5], in addition to cinnamic acid, 2’-hydroxychalcone derivatives that do not contain substituents in the ring “A” and their corresponding flavanones, were analyzed.

In 2’-hydroxychalcone and the corresponding flavanone [4], atoms C-9 have a positive Mulliken charge of approximately +0.4657 and +0.5222, respectively, and in all the analyzed compounds, without exception, atom C-8 has a negative value equal to approximately -0,300. This gave us grounds to conclude that the primary attack of the HO·radical occurs precisely at position C-8 of both cinnamic acid and 2’-hydroxy chalcone, as well as the corresponding flavanone [5, 6].

Table 1 – Derivatives of chalcone, flavanone and flavone, containing a hydroxy group in position 12[*] of the ring “A”[**]



Compounds, No.			Positions of substituents in the ring “B”			
Chalcone	Flavanone	Flavone	1	2	3	4
1x	1anone	1one	H	H	H	H
2x	2anone	2one	OH	H	H	H
3x	3anone	3one	CH_3O	H	H	H
4x	4anone	4one	H	OH	H	H
5x	5anone	5one	H	CH_3O	H	H
6x	6anone	6one	H	H	OH	H
7x	7anone	7one	H	H	CH_3O	H
8x	8anone	8one	H	OH	OH	OH
9x	9anone	9one	H	CH_3O	OH	H
10x	1anone	10one	H	OH	CH_3O	H
11x	11anone	11one	H	CH_3O	CH_3O	H
12x	12anone	12one	H	OH	OH	OH
13x	13anone	13one	H	CH_3O	CH_3O	CH_3O
14x	14anone	14one	H	$(CH_3)_3C$	CH_3O	$(CH_3)_3C$

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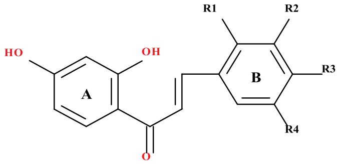
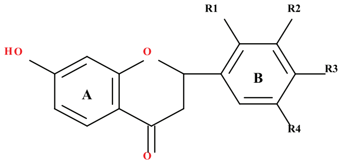
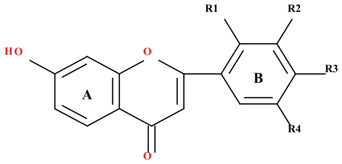
[*] Note. The numbering of carbon atoms is given in accordance with the programs generated by the calculation.

[**] Note. The scheme is presented in accordance with [6]

Table 2 – Values of Mulliken charges on atom C-8 of the cinnamoyl fragment of the2’,4’-dihydroxychalcone (I), 7-hydroxyflavanone (II), 7-hydroxyflavone (III) derivatives containing the same substituents in the ring “B”

			Structures of the analyzed compounds		
N1*	The position of the substituents in the ring «B»		 I a.e.	 II a.e.	 III a.e.
1	R_1=R_2=R_3=R_4=H	−0.3194	−0.3190	−0.4406	−0.4248
2	R_1=OH. R_2=R_3=R_4=H	−0.3647	−0.3640	−0.4486	−0.4265
3	R_1=OCH_3. R_2=R_3=R_4=H	−0.3680	−0.3674	−0.4415	−0.4342
4	R_2=OH. R_1=R_3=R_4=H	−0.2996	−0.2996	−0.4359	−0.4113
5	R_2=OCH_3. R_1=R_3=R_4=H	−0.3037	−0.3032	−0.4355	−0.4141
6	R_3=OH. R_1=R_2=R_4=H	−0.3373	−0.3370	−0.4424	−0.4423
7	R_3=OCH_3. R_1=R_2=R_4=H	−0.3427	−0.3425	−0.4414	−0.4466
8	R_2=R_3=OH. R_1=R_4=H	−0.3243	−0.3239	−0.4396	−0.4282
9	R_2=OCH_3. R_3=OH. R_1=R_4=H	−0.3288	−0.3284	−0.4370	−0.4304
10	R_2=OH. R_3=OCH_3. R_1=R_4=H	−0.3276	−0.3274	−0.4387	−0.4315
11	R_2=R_3=OCH_3. R_1=R_4=H	−0.3329	−0.3327	−0.4380	−0.4341
12	R_2=R_3=R_4=OH. R_1=H	−0.3016	−0.3012	−0.4342	−0.4158
13	R_2=R_3=R_4=OCH_3. R_1=H	−0.3190	−0.3130	−0.4378	-0.4495
14	R_2=R_4=$(CH_3)_3$C. R_3=OH. R_4=H	−0.3467	−0.3454	−0.4379	−0.4179

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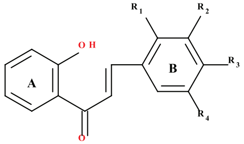
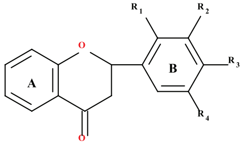
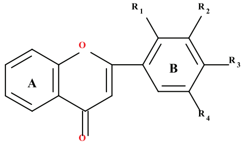
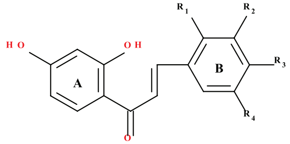
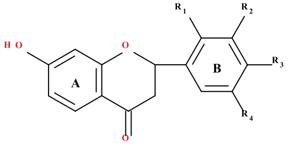
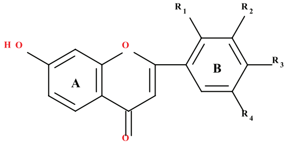
* According to the nomenclature generally accepted for flavonoids, the structures in question should be designated as 7-hydroxy flavanones and 7 hydroxy flavones. Number 12 in brackets indicates the position generated by the calculation program.

Table 3 – Electronic density on atom C-8 of the cinnamoyl fragment of 2'-hydroxychalcone (I), flavanone (II), flavone (III), 2',4'-dihydroxychalcone (IV), 7-hydroxy flavanone (V), 7-hydroxyflavone (VI) derivatives containing the identical substituents in the ring "B"

N		Structures of the analyzed compounds					
		 I	 II	 III	 IV	 V	 VI
1	R_1=R_2=R_3=R_4=H	4.3195	4.4400	4.4320	4.3190	4.4406	4.4249
2	R_1=OH. R_2=R_3=R_4=H	4.3648	4.4468	4.4326	4.3640	4.4487	4.4266
3	R_1=OCH_3. R_2=R_3=R_4=H	4.3681	4.4394	4.4412	4.3675	4.4416	4.4343
4	R_2=OH. R_1=R_3=R_4=H	4.2997	4.4374	4.4186	4.2994	4.4359	4.4113
5	R_2=OCH_3. R_1=R_3=R_4=H	4.3037	4.4365	4.4214	4.3033	4.4355	4.4142
6	R_3=OH. R_1=R_2=R_4=H	4.3373	4.4413	4.4491	4.3370	4.4425	4.4423
7	R_3=OCH_3. R_1=R_2=R_4=H	4.3428	4.4406	4.4532	4.3425	4.4414	4.4466
8	R_2=R_3=OH. R_1=R_4=H	4.3244	4.4373	4.4347	4.3239	4.4397	4.4282
9	R_2=OCH_3. R_3=OH. R_1=R_4=H	4.3288	4.4357	4.4373	4.3284	4.4371	4.4304
10	R_2=OH. R_3=OCH_3. R_1=R_4=H	4.3277	4.4383	4.4386	4.3275	4.4387	4.4316
11	R_2=R_3=OCH_3. R_1=R_4=H	4.3329	4.4376	4.4412	4.3327	4.4382	4.4342
12	R_2=R_3=R_4=OH. R_1=H	4.3017	4.4337	4.4233	4.3013	4.4343	4.4158
13	R_2=R_3=R_4=OCH_3. R_1=H	4.3136	4.4370	4.4355	4.3130	4.4378	4.4495
14	R_2=R_4=$(CH_3)_3C$. R_3=OH. R_4=H	4.3468	4.4401	4.4558	4.3455	4.4380	4.4179

In this report, derivatives of 2’,4’-dihydroxychalcone are considered. During heterocyclization, they turn into 7 (12)-hydroxyflavanones*, respectively.

Heterocyclization of 2’,4’-dihydroxychalcone to the corresponding 7-hydroxyflavanone and then to 7-hydroxyflavone causes changes in the values of Mulliken charges on atoms C-1 – C-8. In the absence of substituents in the ring “B”, all three types of structures on atoms C-1 – C-6 and C-8 have a Mulliken charge of a negative value. If there is a substituent (OH or OCH_3) in positions C-1 and/or C-3 of the “B” ring (compounds 2x–7x; 2anone–7anone; 2one–7one) in atom C-8, the negative Mulliken charge increases substantially, reaching a maximum of –0.4420 (on average) in flavanone (compounds 2anone, 3anone, 6anone, 7anone) and –0.4374 (on average) in flavone (compounds 2one, 3one, 6one, 7one). In corresponding chalcones, the Mulliken charge on atoms C-8 averages –0.3527 (compounds 2x, 3x, 6x, 7x). On atoms C-1 (compounds 2x, 3x, 2anone, 3anone, 2one, 3one) the charge is positive and equals to +0.3244 on average (compounds 2x and 3x), +0.2700 (compounds 2anone and 3anone) and +0, 3191 (compounds 2one, 3one). A similar picture is observed for compounds 4x, 5x, 4anone, 5anone, 8anone – 13anone, 5one – 12one and 14one. On atoms C-3 (compounds 6x – 14x, 6anone– 13 anone, 8one–12one) and practically on all atoms C-7 (except compounds 4x, 8x – 10x, 12x, 13x), the charge has also a positive value.

The changes in the values of Mulliken charges on atoms C-8 for chalcone derivatives (compounds 1x – 14x), flavanone (compounds 1anone– 14anone) and flavone (compounds 1one– 14one), follow the same pattern: for the compounds containing hydroxy- and methoxy groups in position C-1 of the “B” ring (*ortho*-position to the main conjugation chain); the average charge is equal to –0.3657 (compounds 2x, 3x), –0.4450 (compounds 2anone, 3anone) and –0.4304 (compounds 2one, 3one) (Table 2).

On carbon atoms which the electron-donating OH and OCH3-groups are bound with, the Mulliken charge has a positive value of +0.3406 (compound 2x), +0.2845 (compound 6anone) and +0.3476 (compound 2one).

There is a similar picture in case if -OH and $-OCH_3$ groups are located in position C-3 of the ring “B” (*para*-position to the main conjugation chain): in chalcones 6x and 7x, the Mulliken charge on C-8 is equal to -0,3370 and -0.3425, respectively; in flavanones 6anone and 7anone – -0.4424 and –0.4414, in flavones 6one and 7one –0.4423 and -0.4466, respectively. Chalcone derivatives 8x – 11x, flavanones 8anone – 11anone and flavanones 8one– 11one in positions 2 and 3 of the ring “B” simultaneously contain two substituents: 2,3-dihydroxy-, 2-methoxy-3-hydroxy-, 2-hydroxy-3-methoxy- and 2,3-dimethoxy-. In these compounds, the Mulliken charge on C-8 varies slightly: on chalcones 8x – 11x, it is on average equal to –0.3281, for flavanones 8anone–11anone, it averages -0.4385, for flavones 8one– 11one a.e. -0,4310.

The Mulliken charge on C-8 in compounds 6x, 7x (chalcones), 6anone, 7anone (flavanones), 6one, 7one (flavones) containing one substituent (OH or OCH_3) in position 3 of the ring “B”, significantly higher than for compounds 8x – 11x (chalcones), 8anone– 11anone (flavanones) and 8one– 11one (flavones), which contain OH and OCH_3 groups in positions 2,3. It is clear that when there is one substituent in C-3, the polar conjugation with the propenone fragment is much higher than with two substituents in positions C-2 and C-3 simultaneously. This fact is explained by the competing contribution of the substituent in C-2 with that in C-3, which can be seen when comparing the contribution of Taft σ-constants: OH meta +0.127; OH para -0.370; OCH_3 meta +0.115; OCH_3 para -0,268 [7, 8].

Each of the compounds 13x, 14x, 13anone, 14anone, 13one, 14one contains three substituents in positions 2, 3, 4 and, despite the competitive contribution of Taft σ-constants, are characterized by approximately the same values of Mulliken charge on C-8.

It should be notified that on carbonyl carbon C-9, the Mulliken charge is characterized by a high positive value for all the analyzed compounds, and it is in the range from 0.5200 to 0.5335. Based on the data in Table 2, the following can be postulated:

1. the value of Mulliken charges on cinnamoyl fragment C-8 in chalcones in pairs (compounds I and IV), is almost the same (there are differences in the fourth decimal place after the comma). It means that the -OH group in position 4’ (compound IV) has almost no effects on the charge of atom C-8;
2. derivatives of 2’,4’-dihydroxychalcons (compounds 1x, 4x, 5x, 10x, 12x, 13x) have a very slight negative charge on atom C-7 (-0,0180 on average); here, the electron-donor substituents OH and OCH_3 are in positions C-1 or C-3 of the ring “B”;
3. heterocyclization of the chalcones to the corresponding flavanones and flavones contributes to an increase in the negative charge on C-8, which is associated with the involvement of the oxygen heteroatom in the process of transferring electronic effects;
4. the negative charge on C-8 in flavanones (structures II and V) is significantly higher than that of the corre-

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* According to the nomenclature generally accepted for flavonoids, the structures in question should be designated as 7-hydroxy flavanones and 7 hydroxy flavones. Number 12 in brackets indicates the position generated by the calculation program.

sponding flavones (structures III and VI): there is no vinyl group C-7 – C-8 in flavanones;

5. if we compare the positive charge on atoms C-7 of the analyzed compounds, it is easy to see that this charge is almost twice lower in flavanones than in flavones;
6. the above listed features of the distribution of the Mulliken charges indicate that the electrophilic hydroxyl radical is primarily attached to C-8 position.

Electrondensity

When discussing the chemical properties of organic compounds containing fragments with conjugated bonds, not only the charge distribution on the reaction sites, but also the electron density on carbon atoms are helpful.

Analyzing our data on the electron density on the carbon atoms of the cinnamoyl fragment, it can be concluded that using the relationship between the Mulliken charge (q_μ) of the given atom, its electron density ($P\mu\mu$), and the number of electrons introduced by this atom into the total π-system (η_μ), any of these parameters can be determined using this expression [9-11]:

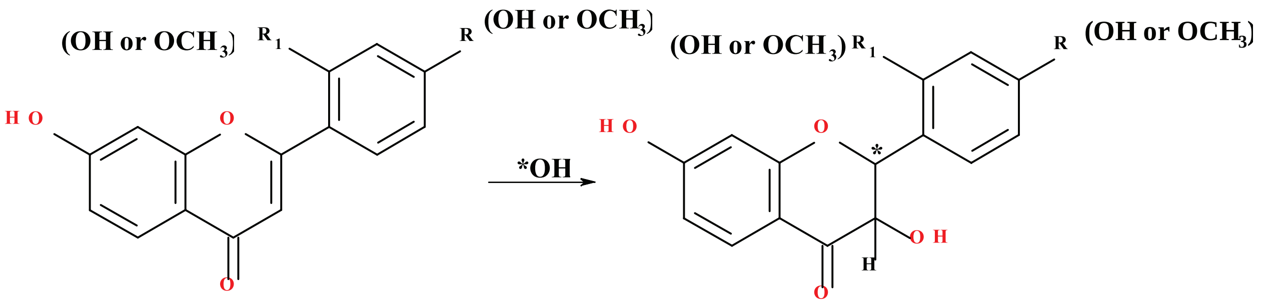
$$q_\mu = \eta_\mu - P\mu\mu$$

Comparing the data presented in Tables 2, 3 and 4, as well as those given in Report I, we found that all atoms of C-7 – C-8 – C-9 propenone unit contribute 4 electrons to form the π-system. Note that the electron density for all compounds is 4 – (a.e.), as can be easily seen from the data in Table 3. For example, if a.e. = –0.26842, then the electron density = 4 – (–0.26842) = 4.2684; if a.e. = + 0.34766, then the electron density= 4 – 0.34766 = 3.6523.

In all the analyzed groups of compounds (including those presented in Report I), the highest electron density in the ring “B” bond system → C-7 → C-8 → C-9 is focused on C-8. Analyzing the values of electron densities on C-8 compounds considered in this article, and those previously given in Report 1, it can be noticed that the presence of hydroxy groups in the ring “A” (position 4’ in chalcones and 7 in flavanones and flavones) practically does not affect the value of this parameter. For comparison, Table 4 presents the values of electron densities for C-8 compounds containing electron-donating substituents in position 1–4 of the ring “B”.[*]

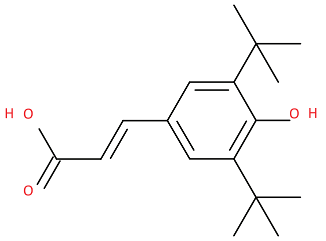
The data of Table 3 show that the electron density values of C-8 in 2’-hydroxy- and 2’,4’-dihydroxychalcones are almost the same, identical to Mulliken charges (Table 2). The same dependence is observed in both flavanone derivatives that do not contain a hydroxy group in the “A” ring, and 7-hydroxy flavanones; these compounds lack the C-7→C-8 vinyl group. The absence of the latter, formally excludes the influence of the +M effect from the electron-donating substituents of the ring “B” on the C-6→C-7→C-8 chain of carbon atoms; however, the presence of an oxygen heteroatom can be the cause for the assumption of its participation in the transmission of electronic effects in the following chain order; C-6→C-7→ → ring “A”. This assumption is true, since the electron densities in C-8 of flavanones and flavones are very close (Table 3).

Thus, taking into account the electrophilic properties of the hydroxyl radical, as well as the magnitude of Mulliken charges and electron densities, the addition of radical $^{\cdot}$OH primarily from the C-8 position, is highly likely. It can be represented as the following diagram:



This scheme is consistent with the conclusions in [13, 14], obtained on the basis of calculations of the enthalpies of radical adducts formation.

Earlier, in accordance with the forecast, we obtained a cinnamic acid derivative, which contained tert-butyl radicals in positions C-2 and C-4 and a hydroxy group in C-3, in the aryl residue of the main conjugation chain (the ring “B”). [12] It showed high cerebroprotective, antioxidant, endothelioprotective and actoprotective activities [15–18]:



4-hydrohy-3,5-di-tert-butyl cinnamic acid

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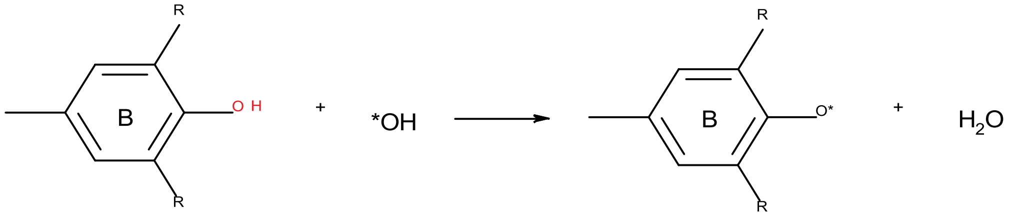
[*] To compare the data, Table 3 includes electron densities for a 2’-OH-chalcone and the unsubstituted flavanone on the “A” ring.

Such a high activity can be explained both by the presence of a sterically hindered hydroxy group in C-3, and by a high electron density (- 4.3252) in C-8. According to the updated data, the Gibbs energy of homolytic cleavage of the O-H bond is 181.29 kJ/mol.

By the method of molecular dynamics, a simulated reaction according to which a process leading to the formation of a highly active and spatially hindered phenoxyl radical, has been carried out:



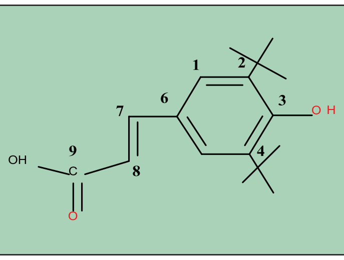
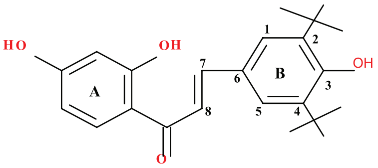
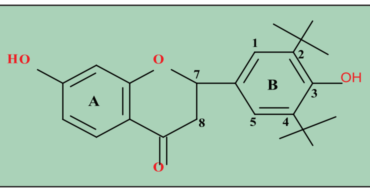
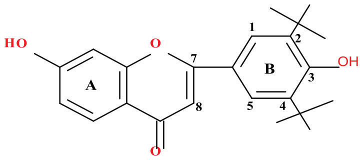
The fact about the cinnamoyl fragment as the main conjugation makes the greatest contribution to the reactivity with respect to reactive oxygen intermediate species (ROIs) and, therefore, to pharmacological activity. It is obvious and undeniable. This conclusion confirms the previously stated results [13,14].

The above listed conclusions were the basis for predicting derivatives of chalcone, flavanone and flavone containing two *tert*-butyl radicals in positions 2,4 and a hydroxy group in C-3 in the aryl residue “B” (Table 1). These compounds are still virtual and will be synthesized in due course time, however, their quantum-chemical characteristics were found necessary to analyze, and the data are shown in Tables 2–4.

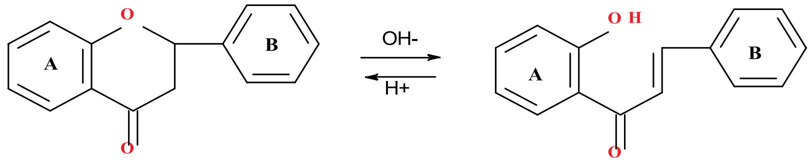
In the previous report it was pointed out that the Gibbs energy of the homolytic bond break H-O depends on the value of the unsaturation index (IUA) of the carbon atom which the hydroxy group is connected with: the higher the IUA value, the lower the bond break energy is.

Considering the closeness of the quantum-chemical characteristics of the predicted structures –14 chalcone, 14flavanone and 14flavone (Table 1) with those of the previously obtained cinnamic acid derivative – it is possible to discuss their high pharmacological activity, which can be proved by the Gibbs energies of the cleavage of the H-O bond (Table 4).

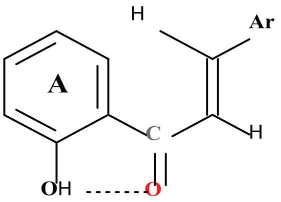
Table 4 – Gibbs free energy of homolytic bond cleavage OH

Structure	IUA unsaturation index (C-3)	Energy of homolytic bond cleavage OH
	0.167	–181.29
	0.166	–178.31
	0.160	–163.08
	0.253	250

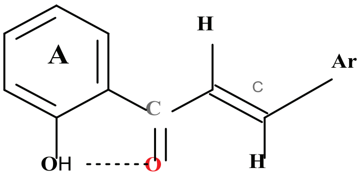
It should be notified that flavanone derivatives belong to systems with a closed conjugation chain. Although flavanones also belong to the closed system, they lack Ar-C=C-C=O conjugation, and for this reason they are able to transform into the corresponding chalcones with a slight PH>7deviation:



For chalcones as compounds with an open conjugation chain, various geometric isomers are possible due to the cross-conjugated system, the most stable of which are the derivatives with the trans configuration of the vinylene fragment [19, 20]:



trans-s-trans



trans-s-cis

Such structural features of chalcones, in contrast to flavones, indicate additional centers of complementarity to the biological substrate, which can explain the presence of a wider spectrum of pharmacological activity, as well as the absence of prooxidant properties [21].

Bond numbers (Nμ) and unsaturation indices (IUA)

In the method of Hückel molecular orbitals (HMO), the values of bond orders [9] are used to characterize molecules, which characterize a relative strength of the covalent bond, its length and reactivity. The sum of all the bond orders belonging to the given atom, determines the bond number (Nμ), which characterizes the degree of saturation of a particular atom. The larger the Nμ value, the higher the degree of saturation, and, conversely, the lower the Nμ value, the greater is the ability of a given atom to form new bonds. This property is closely related to the unsaturation index (IUA) and theoretical valency (Vμ), between which there is a relationship:

$$IUA = V\mu - N\mu$$

Table 5 below examplifies the matrix of quantum chemical parameters obtained by analyzing the compounds considered in this report.

The comparison of the Nμ values on the C-1→C-6→C-7→C-8 site of the cinnamoyl fragment of the analyzed compounds (Table 6), makes it possible to draw a number of conclusions:

1. in the derivatives of 2’,4’-dihydroxychalcone, an increase in Nμ from C-1 to C-7 is observed, which then decreases slightly in C-8;
2. a similar pattern is observed in the derivatives of 7-hydroxyflavanones;
3. in 7-hydroxyflavone, the Nμ values in atoms C-1 and C-6 are almost the same and amount to an average of 3,769, but in C-7 there is an increase in this parameter, which reaches an average of 3,803;
4. in C-8 of 7-hydroxyflavone derivatives, Nμ decreases very sharply and averages 3,696; this indicates an increase in the unsaturation of this atom;
5. based on the data obtained, it can be reliably concluded that reactive oxygen intermediate species (ROIs) will primarily be bound by flavonoids in position C-8 of the propenone fragment.

CONCLUSION

In this report, representatives of the extensive group of natural compounds – flavonoids: chalcones, flavanones and flavones containing electron-donating substituents in the ring “B” (i.e. they are in the aromatic core of the cinnamoyl fragment) – have been considered. All the analyzed structures contain a hydroxy group in the position of 4’-chalcones and in the position of 7-flavanones and flavones [*].

The analysis and comparison of such parameters as the bond number (Nμ), unsaturation index (IUA), and electron density indicate that they differ insignificantly, but a high electron density in C-8 is common to them.

It is characteristic for C-7 atoms in the cinnamoyl fragment C-1→C-6 →C-7→C-8→C-9 of all three types of structures, to have the highest Nμ value and a positive Mulliken charge, and C-8 atoms are characterized by the smallest bond number and the highest electron density. This indicates the fact that the primary attack of the electrophilic radical HO• is most likely to the position of C-8.

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[*] Compounds 14x, 14anon and 14on are not found in nature and so far are virtual. In one of the messages we give methods for their synthesis.

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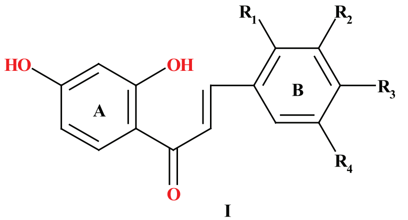
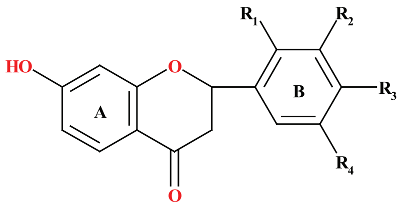
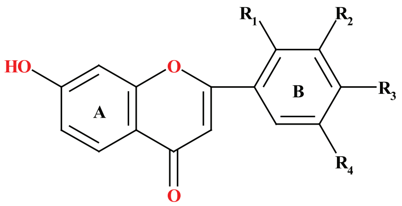
Table 5 – Quantum-chemical parameters of compounds 2x, 2anone and 2one

Substance 2x									
Atom (CV)	1	2	3	4	5	6	7	8	9
Charges, a.e.	0.34062	−0.26842	−0.04754	−0.23754	−0.04850	−0.23270	0.00332	−0.36401	0.54435
Bond numbers (Nμ)	3.747	3.787	3.831	3.841	3.808	3.768	3.841	3.764	3.737
TheoreticalValency (Vμ)	3.900	3.957	3.966	3.967	3.965	3.961	3.930	3.947	3.811
Unsaturation index(IUA)	0.153	0.170	0.135	0.126	0.157	0.193	0.089	0.183	0.074
Electron density	36594	42684	40475	42375	40485	42327	39667	43640	34556
Substance 2anone									
Atom (C_v)	1	2	3	4	5	6	7	8	9
Charges, a.e.	0.28456	−0.23074	−0.91736	0.19793	−0.08918	−0.18985	0.15385	−0.44670	0.52210
Bond numbers (Nμ)	3.777	3.803	3.842	3.844	3.823	3.788	3.829	3.811	3.761
Theoretical valency (Vμ)	3.922	3.966	3.973	3.973	3.968	3.979	3.895	3.928	3.820
Unsaturation index(IUA)	0.145	0.163	0.131	0.129	0.145	0.191	0.066	0.117	0.059
Electron density	3.7154	4.2307	4.0917	4.1979	4.0892	4.1899	3.8461	4.4487	3.4779
Substance 2one									
Atom (CV)	1	2	3	4	5	6	7	8	9
Charges, a.e.	0.34766	−0.26636	−0.04467	−0.23832	−0.03339	−0.25089	0.31826	−0.42655	0.51493
Bond numbers (Nμ)	3.759	3.784	3.833	3.838	3.808	3.727	3.792	3.709	3.792
Theoretical valency (Vμ)	3.904	3.956	3.966	3.967	3.962	3.947	3.901	3.922	3.851
Unsaturation index(IUA)	0.145	0.172	0.133	0.129	0.154	0.220	0.109	0.213	0.059
Electron density	3.6523	4.2664	4.0447	4.2383	4.0334	4.2509	3.6817	4.4266	3.4851

Table 6. Values of bond numbers on carbon atoms *C*-1→*C*-6→*C*-7→*C*-8*

Compound, No.	 I 2’, 4’-dihydroxychalcone				 II 7-OH-flavanone				 III 7-OH-flavone			
	Nμ (C-1)	Nμ (C-6)	Nμ (C-7)	Nμ (C-8)	Nμ (C-1)	Nμ (C-6)	Nμ (C-7)	Nμ (C-8)	Nμ (C-1)	Nμ (C-6)	Nμ (C-7)	Nμ (C-8)
1	3.813	3.859	3.858	3.815	3.829	3.830	3.838	3.818	3.810	3.830	3.802	3.697
2	3.747	3.768	3.841	3.764	3.777	3.788	3.829	3.811	3.759	3.759	3.792	3.709
3	3.740	3.765	3.839	3.787	3.780	3.789	3.843	3.810	3.770	3.742	3.804	3.708
4	3.750	3.763	3.862	3.820	3.763	3.837	3.838	3.815	3.747	3.747	3.807	3.701
5	3.743	3.757	3.860	3.819	3.757	3.838	3.838	3.816	3.740	3.740	3.805	3.701
6	3.812	3.826	3.852	3.807	3.829	3.821	3.838	3.819	3.805	3.805	3.797	3.689
7	3.130	3.819	3.849	3.803	3.826	3.819	3.837	3.819	3.809	3.809	3.794	3.687
8	3.805	3.833	3.857	3.881	3.766	3.833	3.838	3.818	3.749	3.749	3.804	3.695
9	3.808	3.833	3.854	3.809	3.759	3.833	3.838	3.819	3.741	3.721	3.801	3.694
10	3.803	3.832	3.854	3.809	3.767	3.832	3.837	3.818	3.751	3.819	3.837	3.693
11	3.805	3.825	3.851	3.807	3.782	3.825	3.836	3.820	3.743	3.819	3.798	3.692
12	3.740	3.833	3.861	3.818	3.752	3.832	3.838	3.816	3.739	3.826	3.806	3.699
13	3.733	3.837	3.855	3.815	3.727	3.837	3.836	3.821	3.787	3.798	3.788	3.686
14	3.792	3.818	3.848	3.804	3.809	3.818	3.842	3.818	3.725	3.699	3.802	3.699

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* The numbers of the compounds correspond to Table 1

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AUTHORS' CONTRIBUTION

All authors equally contributed to the research work.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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