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Analysis of antioxidant properties of dibenzylideneacetone derivatives using quantum chemical parameters of the molecule

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The antioxidant activity of 10 synthetic dibenzylideneacetone (DBA) derivatives has been studied. Except for the base compound, all other derivatives contain electron-bearing substituents, such as OH and OCH_3, on aromatic fragments. Formally, DBA can be considered a system containing a cinnamoyl moiety linked to a substituted styrene residue.

The aim of the study was to investigate antioxidant properties of the synthesized DBA derivatives and to analyze their quantum chemical parameters revealing the regularities of the «structure–activity» relationship.

Materials and methods. For the carbon atoms of the analyzed compounds, Mulliken charges (AUs), bond numbers (Nms), an unsaturation index (IUA), a free valence index (Fr), a theoretical valence (TV) and the electron density were determined. All calculations were performed on a workstation with an Intel Xeon E5-1620 3.5GHz processor and 20GB RAM using a semi-empirical RM7 method and the WinMopac 2016 software. Ionization energies were calculated using the WinMopac 7.21 software for the studied compounds. The Way2Drug PASS Online predictive program was used to evaluate their possible pharmacological activity. The antioxidant activity was evaluated both *in vitro* (using DPPH and ABTS assays) and *in vivo* (by measuring a superoxide dismutase (SOD) activity and the concentration of products reacting with 2-thiobarbituric acid (TBA-AP) in Wistar rats without pathology).

Results. A preliminary analysis of the possible types of the biological activity of the synthesized DBA derivatives was performed using the Way2Drug PASS Online program. This analysis showed that all the structures have an antitumor activity, which is apparently due to their antioxidant properties. This type of activity was experimentally confirmed by four tests: by DPPH and ABTS *in vitro* and the effect on SOD and by the TBA-AP in animals. The analysis of the data allowed us to determine that the most active antioxidants are compounds 5, 6, and 8, which contain phenolic hydroxyl groups. In these compounds, the 8-hydroxy group is surrounded by OCH_3 radicals on both sides, making it spatially blocked and, therefore, the phenoxyl radical it forms is the most stable. A comparison of the values of the quantum chemical parameters found shows that the most informative for studying the structure–activity relationship are the Mulliken charges (AUs), electron density on carbon atoms, and also their IUA and Fr.

Conclusion. The structural features of the 1,5-diphenylpent-1,4-diene-3-one derivatives and the nature of free radicals formed during biological tests indicate that this class of compounds can be considered promising as antioxidants.

Keywords: quantum chemical parameters, antioxidants, 1,5-diphenylpent-1,4-dien-3-one derivatives, antitumor properties.

Abbreviations: ROS — reactive oxygen species, DPPH — 2,2-diphenyl-1-picrylhydrazyl; ABTS — diammonium salt of 2,2'-azino-bis[3-ethylbenzthiazoline-6-sulfonic acid]; SOD — superoxide dismutase; TBA-AP — thiobarbituric acid active products; IP — ionization potential.

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Анализ антиоксидантных свойств производных дибензилиденацетона с использованием квантовохимических параметров молекул

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Изучена антиоксидантная активность 10 синтетических производных дибензилиденацетона (ДБА), молекула которого представляет собой (1E, 4E)-1,5-дифенилпента-1,4-диен-3-он. За исключением родоначального соединения, остальные содержат в ароматических фрагментах электронодорные заместители — OH, OCH_3. Формально молекулу можно рассматривать как систему, содержащую циннамоильный фрагмент, связанный с остатком замещённого стирола.

Цель. Изучение антиоксидантных свойств синтезированных производных ДБА и их квантовохимических параметров с целью выявления закономерностей взаимосвязи «структура–активность».

Материалы и методы. Для атомов углерода анализируемых соединений определены Малликеновские заряды (а.е.), связевые числа (Nμ), индекс ненасыщенности (IUA), индекс свободной валентности (Fμ), теоретическая валентность (Vμ) и электронная плотность. Все расчёты осуществлены на рабочей станции с процессором IntelXeonE5-1620 3,5 ГГц, 20 Гб оперативной памяти с использованием полуэмпирического метода PM7 (программа WinMopac 2016). Для изучаемых соединений по программе WinMopac 7.21. был рассчитан показатель энергии ионизации. Для оценки возможной фармакологической активности использовалась прогностическая программа Way2Drug PASS Online. Антиоксидантную активность анализируемых соединений оценивали *in vitro* (DPPH и ABTS тесты), а также *in vivo* (определение активности супероксиддисмутазы (СОД) и концентрации активных продуктов, реагирующих с 2-тиобарбитуровой кислотой (ТБК-АП) у крыс линии Wistar без патологии).

Результаты. Предварительно был осуществлён анализ возможных видов биологической активности синтезированных производных ДБА по программе Way2Drug PASS Online который показал, что для всех структур характерна противоопухолевая активность, что, по-видимому, обусловлено в том числе и антиоксидантными свойствами. Данный вид активности экспериментально определялся по 4 тестам — DPPH и ABTS (*in vitro*) и по влиянию на СОД и ТБК-АП (на животных). Анализ полученных данных позволил установить, что наиболее активными антиоксидантами являются соединения 5, 6 и 8, содержащие фенольные гидроксигруппы. В структуре 8 гидроксигруппа с обеих сторон окружена OCH_3-радикалами, то есть она является пространственно затруднённой и, следовательно, образуемый им феноксильный радикал наиболее устойчив. Сопоставление значений найденных квантовохимических параметров показывает, что наиболее информативными с точки зрения изучения взаимосвязи «структура–активность» являются Малликеновские заряды (а.е.), электронная плотность на атомах углерода, а также индексы IUA и Fμ.

Заключение. Структурные особенности полученных производных 1,5-дифенилпента-1,4-диен-3-она, а также природа образуемых свободных радикалов в использованных биологических тестах однозначно свидетельствуют о том, что анализируемый класс соединений можно считать перспективными антиоксидантами.

Ключевые слова: квантовохимические параметры; антиоксиданты; производные 1,5-дифенилпента-1,4-диен-3-она; противоопухолевые свойства

Список сокращений: АФК — активные формы кислорода; DPPH — 2;2-дифенил-1-пикрилгидразил; ABTS — диаммониевая соль 2,2’-азино-бис [3-этилбензтиазолин-6-сульфоновой кислоты; СОД —- супероксиддисмутаза; ТБК-АП – активные продукты тиобарбитуровой кислоты; ИП — ионизационный потенциал.

INTRODUCTION

Currently, extensive experimental data have been accumulated, they clearly indicate a relationship between free radical oxidation processes and metabolic disorders. These processes, as a rule, lead to the suppression of the antioxidant defense mechanisms due to the accumulation of free radicals, including reactive oxygen species (ROS), in the body. Among the latter, the hydroxyl radical (HO•) characterized by electrophilic properties, is the most dangerous. It interacts with the nitrogenous bases of nucleic acids, promoting the formation of numerous mutations [1-4]. The hydroxyl radical simultaneously interacts with phospholipids in the cell membranes, causing tissue damages and various pathological processes in the human body [2, 5–7].

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In the cases of disorders caused by an excessive production of ROS and other free radicals, it is important to search for non-toxic antioxidants. From this perspective, the authors believe that derivatives of 1,5-diphenylpent-1,4-diene-3-one (DBA), which contain two cinnamoyl groups, are of interest. These molecules have the structure shown in Fig. 1.

Previously, the interaction of natural polyphenols, such as cinnamic acid derivatives, with the hydroxyl radical using quantum chemical methods, had been analyzed [8, 9]. A relationship between their biological activity and the presence of a hindered phenol group had also been established [10, 11].

THE AIM of the study was to investigate antioxidant properties of the synthesized DBA derivatives and to analyze their quantum chemical parameters revealing the regularities of the «structure–activity» relationship.

MATERIALS AND METHODS

Study Design

At the first stage of the study, virtual structures for potential target compounds using the Way2Drug PASS Online program (Way2Drug, Russia)[1], were described; that allowed the authors to predict their activity. Then 10 compounds, which had been synthesized by condensing acetone with 2 moles of corresponding aromatic aldehydes in an alkaline environment, were selected. After a five-fold recrystallization, the structures of the compounds were confirmed, and then were studied their antioxidant activity. The study period lasted from 11 November 2023 to 29 May 2024.

Tested compounds

The DBA derivatives were obtained through the alkaline condensation of one mole of acetone and two moles of various aromatic aldehydes, including benzaldehyde, p-hydroxybenzaldehyde, salicylic aldehyde, 4-methoxybenzaldehyde, 2,3-dihydroxybenzaldehyde, vanillin, veratinaldehyde, lilialdehyde, 3,4,5-trimethoxybenzaldehyde, and 2,4,6-trimethoxyphenylacetaldehyde. These compounds contain similarly-named substituents on the aryl fragments. The quantum chemical properties of these target compounds were computed on a workstation equipped with an Intel Xeon E5-1620 processor at a frequency of 3.5 GHz and 20 GB of RAM. The ionization energy of the synthesized molecules was calculated using the WinMOPAC 7.21 software (Russia).

[1] Way2Drug PASS Online. Available from: http:// www. Pharmaexpert.ru/ passonline/

DPPH assay

To assess the ability of the investigated substances to scavenge ингибировать DPPH radicals in a model system, the method proposed by B. Ahmadipour et al., was used [12].

Then 1 ml of the solution (20 mg/mL was the initial solution) of the analyzed substances was incubated in ethanol (Vecton, Russia) at various concentrations in double dilutions, and 0.5 mL of a 0.4 mM solution of DPPH (Sigma-Aldrich, Germany) in methanol (Vecton, Russia) was added for 30 min at room temperature. Then, the optical density change (measured using a PE-5300V spectrophotometer from Ekroschem LLC, Russia at λ=518 nm against pure methanol from Panreac, Spain) of the samples was recorded. The methanol DPPH solution served as a positive control (A_0). The inhibition percentage was calculated using the following formula:

$$\% \text{ ing.} = \frac{A_x}{A_0} \times 100\%,$$

where A_x is the optical density of the sample and A_0 is the optical density of the positive control.

ABTS assay

0.1 mL of the solution (20 mg/mL is the initial concentration) containing the analyzed substances in ethanol (Vecton, Russia), in various concentrations, and 0.19 mL of a 7 mM aqueous solution of ABTS (Sigma-Aldrich, Germany) were incubated for 5 min at room temperature in the dark. After that, the optical density of the samples was measured at λ=734 nm compared to purified water. An aqueous solution of ABTS served as a positive control (A_0). The percentage of the inhibition was calculated using above formula [13].

The *in vivo* study of the antioxidant activity was conducted on 100 male Wistar rats, weighing 200–210 g obtained from the «Rappolovo» laboratory animal nursery (Russia), after a microbiological control and a 2-week quarantine. These animals were kept under standard conditions, including the air temperature between 18–22°C, a relative humidity of 60±5%, with a daily cycle of 12 hours of light and 12 hours of darkness, and a free access to food and water. The design of the study and conditions for the animal care adhered to generally accepted standards for experimental ethics, as outlined in Directive 2010/63/EU, and was approved by the Local Ethics Committee at the Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University (Protocol No. 7 dated 4 April 2024).

For the analysis, the compounds were administered to the animals (*n*=10 per test substance) for a period of 30 days, at a dose of 20 mg/kg, once per day in the form of an *ex tempore* suspension prepared on a water basis, without the use of any additional substances. The experimental groups were: Group 1 — the animals receiving compound 1, Group 2 — the animals receiving compound 2, Group 3 — the animals receiving compound 3, Group 4 — the animals receiving compound 4, Group 5 — the animals receiving compound 5, Group 6 — the animals receiving compound 6, Group 7 — the animals receiving compound 7, Group 8 — the animals receiving compound 8, Group 9 — the animals receiving compound 9, and Group 10 — the animals receiving compound 10.

Afterwards, the blood was collected from the abdominal aorta of rats under chloral hydrate anesthesia (Panreac, Spain; dose 350 mg/kg, intraperitoneally). Then, the blood samples were centrifuged at 3500 rpm for 15 min (Armed centrifuge, Russia) to obtain serum, in which changes in the superoxide dismutase (SOD) activity and concentrations of products reacting with 2-thiobarbituric acid (TBA-AP) were assessed.

Determination of SOD activity

The activity of SOD was estimated using a xanthine oxidase method [14]. The incubation medium consisted of 0.05 mmol/L xanthine, 0.025 mmol/L 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride, 0.94 mmol/L EDTA, 80 U/L xanthine oxidase, and 40 mmol/L CAPS buffer. The extinction of the samples was measured at 505 nm, and the activity of SOD was expressed in U/L.

Determination of TBA-AP concentration

The concentration of TBA-AP was determined using a spectrophotometry at 532 nm. The optical density of the stained product of the reaction between aldehydes and 2-thiobarbituric acid was proportional to the TBA-AP concentration and was expressed in nM/mL [15].

Statistical analysis

A statistical processing of the results obtained was carried out using a software package StatPlus 7.0 (AnalystSoft Inc., USA, license 16887385). The data were expressed as a mean±standard deviation (M±SD). The normality of the data distribution was assessed using the Shapiro–Wilk test. The differences between the groups were determined using ANOVA with the Newman–Keuls post-hoc test (normally distributed data) or the Kruskal–Wallis test with the Dunn post-hoc test (abnormally distributed data) [16].

RESULTS AND DISCUSSION

Endogenous ROS take part in biochemical processes that are regulated by enzymatic and non-enzymatic components in cells. When there is an overproduction of ROS in the body, this disrupts equilibrium processes, leading to uncontrolled chemical reactions that cause damage and death to cells. In these cases, natural and synthetic antioxidants are important [17–19]. Cinnamic acid and its hydroxy and methoxy derivatives are some of the most active natural compounds when it comes to ROS. The hydroxyl radical has significant electrophilic properties and attaches to the C-8 position of cinnamic acid, as this carbon atom has the largest charge and highest electron density among the neighboring carbon atoms [20].

The DBA derivatives analyzed in this report contain two cinnamoyl fragments, or cinnamic acid residues, as their basis. This fact was used to determine the positions in the DBA structure that have electron-donating properties, which neutralize the ROS by donating an electron.

Table 1 shows the structures of the compounds analyzed and their experimentally determined antioxidant activity. It also provides information on the types of the predicted antitumor activities based on the Way2Drug PASS Online program, as well as the manifestation likelihood of these activities.

From the data in Table 1, it can be seen that compounds 5, 6, and 8 have the highest levels of the antioxidant activities.

In the DPPH assay, the IC_{50} value of compound 5 was significantly lower than those of compounds 1–4, 7, 9 and 10, by 79.1, 67.2, 75.3, 70.6, 56.1, and 24.6%, respectively (all *p*-values <0.05). Similarly, in the ABTS assay, the IC_{50} of compound 5 was also significantly lower (p <0.05) than those of the other compounds (Table 1). Additionally, the SOD activities in the rats treated with compound 5 was higher than in those treated with compounds 1–4 and 7, by 41.1, 27.8, 44.9, 23.3, and 41.1% (all *p*-values <0.05), respectively. In these groups, the concentration of TBA-AP was also decreased by 42.3, 37.5, 37.6, 48.3, and 34.8% (all *p*-values <0.05), respectively.

In the DPPH assay, the IC_{50} value of compound 6 was lower than those of compounds 1–4 and 7,9 and 10 by 82.0, 71.8, 78.7, 74.7, 62.2, 34.1, and 33.2%, respectively (all *p*-values <0.05). Similarly, in the ABTS assay, the IC_{50} of compound 6 was lower than the IC_{50} of compounds 1–4, 7, 9, and 10 by 84.2, 71.6, 85.2, 78.1, 63.6, 39.1, and 35.1%, respectively (all *p*-values <0.05). In terms of the animal studies, the activity of SOD was increased in the

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rats treated with compound 6 compared to those treated with compounds 1, 2, and 3 and compound 7, 22.1, 38.4, 17.8, and 34.9%, respectively (all *p*-values <0.05). Additionally, the content of TBA-AP was decreased in the rats treated with compound 6 by 30.8, 25, 25.1, and 21.7%, respectively, compared to the rats treated with the other compounds (all *p*-values <0.05).

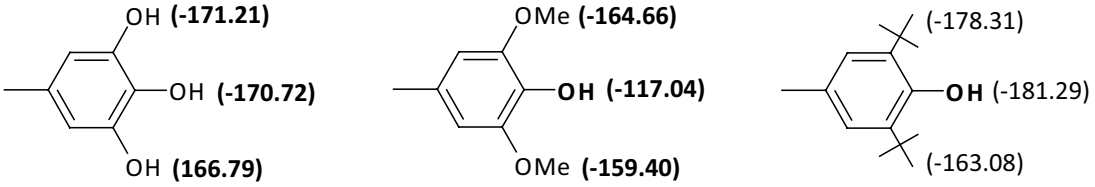
The IC_{50} value of compound 8 in the DPPH and ABTS assays was significantly lower than those of compounds 1 by 84.1 and 87.0% (*p* <0.05); compounds 2 — 75.1 and 76.5% (*p* <0.05); compounds 3 — 81.2 and 87.8% (*p* <0.05); compounds 4 — 77.6 and 81.9% (*p* <0.05); compounds 7 — 66.6 and 69.9% (*p* <0.05); compounds 8 — 42.7 and 49.8% (*p* <.05); compounds 10 — 41.0 and 46.4% (*p* <0.05). It is also worth noting that the activity of serum SOD in rats treated with compound 8 was higher than in animals treated with compounds 1–4 and 7 by 40.6, 27.3, 44.3, 22.8 and 40.6% (all *p*-values <0.05), while the content of TBK-AP decreased by 46.2, 41.7, 41.8, 51.7, and 39.1% (all *p*-values <0.05), respectively.

The analysis of the quantum chemical parameters of the synthesized compounds testifies to the fact that the pentadiene moiety exhibits the highest reactivity. In this moiety, two vinyl groups are separated by a carbonyl carbon atom, indicating the absence of a conjugated double bond.

Free phenolic hydroxyl groups are capable of breaking the H-O bond homolytically and forming phenoxyl radicals. If the hydroxyl group is shielded on both sides, the resulting radical is stabilized and relatively stable [8].

It has been previously experimentally shown that the Gibbs energy of homolytic H-O bond breaking depends not only on the unsaturation index (IUA) and a positive charge of the carbon atom to which the hydroxyl group is attached, but also on the nature of the neighboring substituents. For example, if methoxy groups act as shielding substituents, the Gibbs energy is -117.04. In contrast, if alkyl ditret-butyl groups act as substituents, this energy increases to -181.29.

These results are summarized below:



Bond numbers (Nμ) and free valence indices (Fr)

As it is known, a free valence index is an important tool for analyzing the reactivity of organic compounds. This value, Fr, is typically calculated by subtracting the maximum possible number of bonds (Nm) from the actual number of bonds a carbon atom can form (in this case, 4.732, which corresponds to the maximum "valence" of 4.732) [21–23].

The number of bonds an atom has, Nμ, indicates its saturation level: the more bonds an atom forms, the lower its N value, and vice versa. Table 2 shows the bond numbers (Nm) for the carbon atoms in the aromatic nuclei (positions C-2 to C-3 and C-15 to C-18).

Therefore, if certain atoms do not fully utilize their properties to form bonds, it can be said that they have a certain amount of "free valence". This value indicates a potential for the interaction with reagents lacking a charge dipole.

Fr applies only to sp- and sp^2-hybridized carbon atoms, and not to C atoms that can form σ-bonds. If, for example, the Fr value is 0.732 (for an ethylene carbon atom), this indicates that the atom is highly reactive in reactions involving the addition of neutral particles. Atoms with Fr >1 values are more likely to attach free radicals.

Tables 3 and 4 provide the Fμ values for atoms 7, 8, 11, and 12 in the pentadienone fragment, as well as for aryl-C-2-C-5 and C-15-C-18.

The data presented show the following.

1. The Fr values of carbon atoms (C-7, C-8, C-11, and C-12) in the pentadienone fragment are very similar and range from 0.781 to 0.815.
2. The Fr indices for C2 aromatic nuclei (C-2-C-5 and C-15-C-18) differ depending on the substituent connected to them. In compound 5, with two OH groups connected to atoms C-4, C-5 (ring "A") and C-17, C-18 (ring "B"), the Fμ values are in the range of 0.813-0.830. For the remaining atoms — C-2, C-3, and C-15, C-16 — they are approximately the same and range from 0.780 to 0.790.
3. In compound 6, the phenolic hydroxyl group is bound to C-3 (ring "A"), with an Fr value of 0.830; it is also bound to C-16, with an Fμ of 0.823. The Fr values for C-4 and C-17 are 0.819 and 0.820, respectively.
4. In the most active compound, hydroxyl groups

are associated with C-3 (ring "A") and C-16 (ring "B"). The magnitude of Fr on these atoms is 0.807 and 0.838, respectively.

5. It is characteristic of compounds 4, 6, 7 and 8 to have aryl carbon atoms associated with OCH_3 groups. Atoms C-3 and C-16 (compound 4), C-4 and C-17 (compound 6), C-3, C-4, and C-16 and C-17 (compound 7), and C-2, C-4 and C-15 and C-17 (compound 8) have positive Mulliken charges in the range of 0.1024 to 0.1600. The carbonyl carbon atom (C-9), on the other hand, has the highest positive charge, equal to 0.4600±0.0045 in compounds 5, 6 and 8, and reaching up to 0.4725±0.0025 in compounds 1–4 and 7.

Electron density and electronic effects of substituents

The distribution of the electron density in the analyzed molecules depends on the electronic effects of substituents that are conjugated with the pentadienone fragment in the aromatic nuclei. This unevenness in the electron density distribution suggests the presence of reactive centers in the molecule. These centers determine the direction of the attack by other molecules or agents. If the latter is of a radical nature (the presence of an unpaired electron), then, being highly reactive, it (the agent) has little sensitivity to the electron density distribution.-

When analyzing this parameter for the DBA derivatives, the pentadienone fragment and its associated aryl residues A and B, taking into account the "+mesomeric effect" of electron-donating substituents, were considered. Tables 3 and 4 show the values of the electron density on the carbon atoms of the pentadiene fragment (C-7, C-8 and C-11, C-12), as well as the aromatic fragments "A" (C-2-C-5) and "B" (C-15-C-18).

In the unsubstituted parent structure, the electron density is distributed as follows: C-7 — 4.080; C-8 — 4.279; C-11 — 4.31; C-12 — 4.039. On the carbon atoms of aromatic fragments "A" and "B", the electron densities are almost the same: C-2 and C-15 — 4.154; C-3 and C-16 — 4.134; C-4 and C-17 — 4.156; and C-5 and C-18 — 4.142, with the differences appearing only on the third decimal place.

The introduction of hydroxyl groups in positions C-3 and C-16 (which are para-positions relative to C-7 and C-12, respectively) increases the electron density on atoms C-8 and C-11 of the pentadienone fragment (compound 2). A similar pattern is observed when OH groups are located in positions 5 and 18 (compound 3). However, if the OCH_3 group replaces OH in positions C-3 and C-16 (para-positions to C-7 and C-12), the values of the electron density on C-8 and C-12 remain practically unchanged.

The $\bar{\sigma}$-Taft substituent constants are presented in Table 5 [24].

In compound 5, dihydroxy groups are located in positions C-4 and C-5 (core "A"), as well as in C-17 and C-18 (core "B"). In C-5 and C-18, the OH groups with respect to the pentadienones C-7 and C-12, occupy ortho positions and the σ constant is 0.370; and the OH groups in C-4 and C-17 are located in meta positions with respect to C-7 and C-12 of the pentadienone fragments and their $\bar{\sigma}$ =+0.127. Thus, the total contribution of phenolic hydroxy groups (2 in each core) is:

$$\sum\bar{\sigma} = 2 \times (-0.370) + 2 \times (+0.127) = -0.486$$

Compound 6 has OH groups in the para-positions to C-7 and C-12. C-3 and C-16 have OH groups; but in the meta-positions to C-7 and C-12, there are methoxy groups, so, here the total contribution of two meta-OCH_3 and two para-OH is equal to:

$$\sum\bar{\sigma} = 2 \times (-0.370) + 2 \times (+0.115) = -0.510$$

The most antioxidant active compound 8 contains two shielded hydroxy groups in positions C-3 (core "A") and C-16 (core "B"). In addition to these OH groups, there are two methoxy groups in ortho positions to C-2, C-4 (core "A") and C-15, C-17 (core "B") atoms. These substituents are located in meta positions with respect to the C-7 and C-12 atoms of the pentadienone fragment. The total contribution of the two shielded OH groups in C-3 and C-16 and four methoxy groups in positions 2,4 (core "A") and 15,17 (core "B") is:

$$\sum\bar{\sigma} = 2 \times (-0.370) + 4 \times (+0.115) = -0.280$$

Ionization potential

In the analyzed DBA derivatives, the pentadienone fragment contains electron-redundant centers at C-7, C-8, C-11, and C-12 atoms, which can become electron donors in redox reactions. The energy that is used to detach one electron from a molecule is called the first ionization potential (IP). The lower the IP, the easier it is for the molecule to release an electron, turning into a positively charged ion, i.e., it transitions to an excited state. Table 3 shows the ionization potentials for all 10 synthesized DBA derivatives, which means that the most antioxidant active compounds (5, 6, and 8) are characterized by IP values of 8 987, 8 714, and 8 639, respectively.

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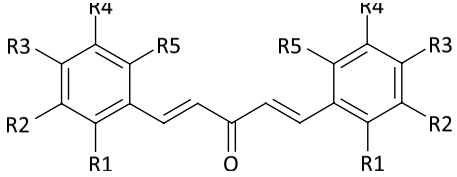
Table 1 – Structures of synthesized derivatives of (5E, 8E) 7,12 (bisphenyl) penta-7,11-diene-3-one* and their biological activities



Compounds, No. in sequence	R mean	Antioxidant activities				Probability of antitumor activities according to Way2Drug PASS Online, %			
		in vitro	*in vitro*	*in vivo*	*in vivo*	Breast cancer	Lung cancer	Cervical cancer	Free radical scavengers
		DPPH, IC_{50} mM/mL	ABTS, IC_{50} mM/mL	SOD, U/L	TBA-AP, nM/mL				
1	$R_1=R_2=R_3=R_4=R_5=H$	76.1±0.29*#Δ	79.8±0.21*#Δ	262.7±10.9*#Δ	2.6±0.5*#Δ	70.3	71.6	–	–
2	$R_1=R_2=R_4=R_5=H$ $R_3=OH$	48.5±1.2*#Δ	44.3±0.31*#Δ	290±9.2*#Δ	2.4±0.2*#Δ	67.3	55.7	–	55.2
3	$R_1=R_2=R_3=R_4=H$ $R_5=OH$	64.3±0.9*#Δ	85.1±0.5*#Δ	255.9±26.4*#Δ	2.4±0.4*#Δ	63.9	–	–	54.0
4	$R_1=R_2=R_4=R_5=H$ $R_3=OCH_3$	54.1±0.3*#Δ	57.6±0.6*#Δ	300.7±8.4*	2.9±0.9*	68.1	65.2	–	50.1
5	$R_1=R_2=R_3=H$ $R_4=R_5=OH$	15.9±0.4	16.7±0.8	370.7±9.4	1.5±0.2	66.1	54.7	53.9	58.2
6	$R_1=R_2=R_4=H$ $R_3=OH$; $R_4=OCH_3$	13.7±0.1	12.6±0.5	354.2±7.2	1.8±0.1	66.9	56.6	53.6	68.4
7	$R_1=R_2=R_5=H$ $R_3=R_4=OCH_3$	36.2±0.7*#Δ	34.6±0.9*#Δ	262.7±10.9*#Δ	2.3±0.2*#Δ	69.8	64.5	59.9	54.9
8	$R_1=R_5=H$ $R_2=R_4=OCH_3$; $R_3=OH$	12.1±0.2	10.4±0.6	369.3±14.5	1.4±0.1	67.6	65.0	55.9	66.9
9	$R_1=R_5=H$ $R_2=R_3=R_4=OCH_3$	21.1±0.64*#Δ	20.7±0.27*#Δ	326.9±12.5	1.7±0.1	79.1	79.1	70.1	55.5
10	$R_2=R_4=H$ $R_1=R_3=R_5=OCH_3$	20.5±0.5*#Δ	19.4±0.42*#Δ	354.7±11.7	1.5±0.1	69.9	57.6	–	–

Note: DPPH — 2,2-diphenyl-1-picrylhydrazyl; ABTS — diammonium salt of 2,2'-azino-bis [3-ethylbenzthiazoline-6-sulfonic acid; SOD — superoxide dismutase; TBA-AP — active products reacting with 2-thiobarbituric acid; * reliably relative to compound 5 (Newman-Keuls test, p <0.05); # reliable relative to compound 6 (Newman-Keuls test, p <0.05); Δ reliable relative to compound 8 (Newman-Keuls test, p <0.05). When forming the structures of molecules for computer calculations, the program itself numbered the positions of the atoms. All compounds were obtained by an alkaline condensation of acetone with 2 mol substituted benzaldehydes, and therefore, the R values in the aromatic nuclei are the same.

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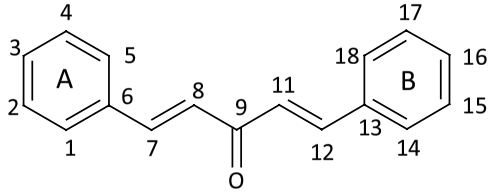
Table 2 – Mulliken charges (AU) and bond numbers (Nμ) on carbon atoms of aromatic nuclei with which OH groups are associated



Compounds, No. in sequence	Position of hydroxyl group								Mulliken charges on carbon atom								Bond numbers (Nμ)							
	2	3	4	5	15	16	17	18	C-2	C-3	C-4	C-5	C-15	C-16	C-17	C-18	C-2	C-3	C-4	C-5	C-15	C-16	C-17	C-18
1	–	–	–	–	–	–	–	–	-0.154	-0.134	-0.156	-0.142	-0.155	-0.131	-0.159	-0.128	3.962	3.961	3.961	3.957	3.962	3.960	3.962	3.952
2	–	+	–	–	–	+	–	–	-0.256	0.308	-0.322	-0.059	-0.256	0.312	-0.327	-0.045	3.935	3.882	3.925	3.945	3.934	3.881	3.925	3.940
3	–	–	–	+	–	–	–	+	-0.231	-0.060	-0.259	0.303	-0.238	-0.06	-0.258	0.314	3.943	3.943	3.938	3.879	3.945	3.941	3.938	3.878
5	–	–	+	+	–	–	+	+	-0.148	-0.183	0.196	0.144	-0.155	-0.180	0.196	0.158	3.952	3.947	3.918	3.961	3.953	3.938	3.919	3.905
6	–	+	–	–	–	+	–	–	-0.201	0.206	0.102	-0.229	0.206	0.215	0.095	-0.209	3.936	3.902	3.913	3.936	3.935	3.909	3.912	3.930
8	–	+	–	–	–	–	–	–	-0.199	0.081	0.159	-0.299	0.214	0.054	0.168	-0.290	3.925	3.911	3.916	3.923	3.964	3.894	3.909	3.918

Table 3 – Ionization potentials of dibenzylidenacetone derivatives, values of unsaturation indices (IUA), electron density, and free valence indices (Fr) on atoms of C-7, C-8, C-11, and C-12 of the pentadienone fragment of compounds 1–10

Compounds, No. in sequence	R	IUA				Electronic density				Fμ				Ionization potential
		C-7	C-8	C-11	C-12	C-7	C-8	C-11	C-12	C-7	C-8	C-11	C-12	
1	$R_1=R_2=R_3=R_4=R_5=H$	0.028	0.01	0.012	0.029	4.080	4.279	4.313	4.039	0.791	0.779	0.784	0.81	9.457
2	$R_1=R_2=R_4=R_5=H$ $R_3=OH$	0.028	0.015	0.018	0.031	4.061	4.294	4.332	4.017	0.791	0.786	0.793	0.814	9.022
3	$R_1=R_2=R_3=R_4=H$ $R_5=OH$	0.038	0.019	0.021	0.032	4.057	4.283	4.323	4.012	0.794	0.79	0.796	0.805	9.195
4	$R_1=R_2=R_4=R_5=H$ $R_3=OCH_3$	0.029	0.014	0.017	0.031	4.057	4.297	4.336	4.013	0.792	0.785	0.793	0.815	8.791
5	$R_1=R_2=R_3=H$ $R_4=R_5=OH$	0.037	0.014	0.019	0.042	4.069	4.268	4.308	4.022	0.792	0.784	0.79	0.813	8.987
6	$R_1=R_2=R_4=H$ $R_3=OH$; $R_4=OCH_3$	0.035	0.021	0.015	0.029	4.093	4.273	4.326	4.025	0.795	0.789	0.789	0.81	8.714
7	$R_1=R_2=R_5=H$ $R_3=R_4=OCH_3$	0.03	0.013	0.017	0.033	4.065	4.287	4.329	4.017	0.792	0.783	0.791	0.817	8.570
8	$R_1=R_5=H$ $R_2=R_4=OCH_3$; $R_3=OH$	0.035	0.017	0.021	0.029	4.100	4.269	4.3152	4.029	0.796	0.784	0.794	0.81	8.639
9	$R_1=R_5=H$ $R_2=R_3=R_4=OCH_3$	0.036	0.018	0.022	0.03	4.105	4.258	4.304	4.044	0.796	0.785	0.793	0.807	8.779
10	$R_2=R_4=H$ $R_1=R_3=R_5=OCH_3$	0.03	0.033	0.035	0.033	4.021	4.302	4.331	3.980	0.8	0.806	0.812	0.815	8.629

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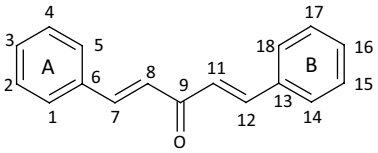
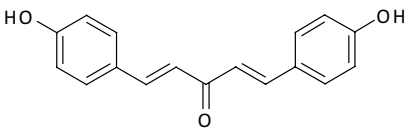
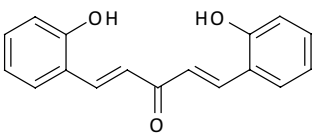
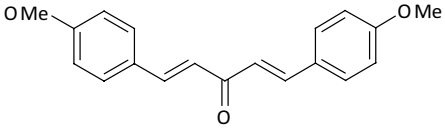
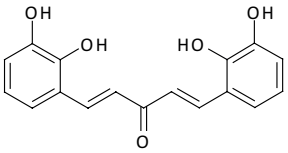
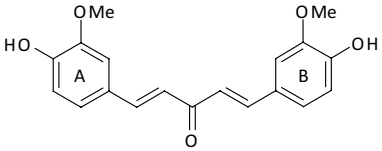
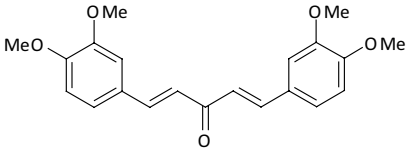
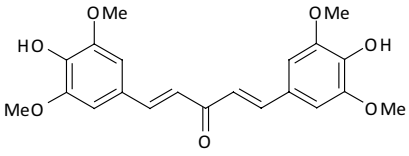
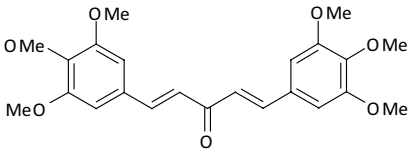
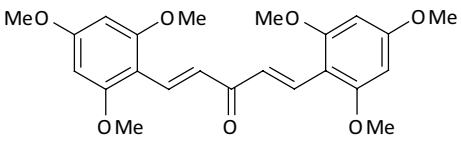
Table 4 – Values of unsaturation indices (IUA), electron density, and free valence indices (Fr) of carbon atoms of aromatic nuclei A and B

Compounds, No. in sequence	Nucleus A										Nucleus B									
	IUA				Electronic density				Fμ				IUA				Electronic density				Fμ	
	C-2	C-3	C-4	C-5	C-2	C-3	C-4	C-5	C-2	C-3	C-4	C-5	C-15	C-16	C-17	C-18	C-15	C-16	C-17	C-18	C-15	C-16	C-17	C-18
1	0.014	0.015	0.015	0.019	4.154	4.134	4.156	4.142	0.77	0.771	0.771	0.775	0.014	0.016	0.014	0.023	4.155	4.130	4.159	4.128	0.77	0.772	0.77	0.78
2	0.022	0.027	0.027	0.025	4.256	3.692	4.322	4.059	0.797	0.85	0.807	0.787	0.023	0.027	0.025	0.027	4.256	3.688	4.326	4.045	0.798	0.851	0.807	0.792
3	0.022	0.025	0.02	0.03	4.231	4.060	4.258	3.696	0.785	0.789	0.794	0.853	0.023	0.027	0.019	0.03	4.238	4.055	4.258	3.686	0.787	0.791	0.794	0.854
4	0.023	0.03	0.031	0.023	4.263	3.732	4.313	4.064	0.798	0.836	0.811	0.785	0.024	0.031	0.029	0.028	4.262	3.728	4.317	4.049	0.799	0.838	0.81	0.792
5	0.022	0.019	0.021	0.029	4.148	4.183	3.804	3.856	0.78	0.785	0.814	0.831	0.021	0.029	0.021	0.028	4.155	4.179	3.803	3.842	0.779	0.794	0.813	0.827
6	0.028	0.034	0.035	0.031	4.201	3.794	3.897	4.228	0.796	0.83	0.819	0.796	0.028	0.026	0.036	0.039	4.205	3.785	3.905	4.209	0.797	0.823	0.82	0.802
7	0.031	0.032	0.04	0.036	4.217	3.821	3.893	4.227	0.80	0.815	0.822	0.799	0.031	0.034	0.04	0.041	4.217	3.817	3.899	4.208	0.8	0.818	0.823	0.803
8	0.027	0.032	0.031	0.026	3.801	3.919	3.841	4.299	0.807	0.821	0.816	0.809	0.044	0.039	0.036	0.032	3.786	3.946	3.832	4.291	0.828	0.838	0.823	0.814
9	0.037	0.037	0.042	0.028	3.751	4.050	3.763	4.358	0.833	0.839	0.839	0.830	0.036	0.041	0.044	0.033	3.753	4.043	3.768	4.342	0.831	0.84	0.84	0.83
10	0.024	0.049	0.024	0.045	4.471	3.626	4.511	3.639	0.886	0.883	0.899	0.875	0.025	0.049	0.032	0.049	4.470	3.624	4.512	3.635	0.887	0.884	0.908	0.877

Table 5 – Constant substituents for substituted phenyls

Compounds		σ̄-Taft substituent constants						∑σ̄ calculated
No.	Structure	OH-П -0.370	OH–O -0.370	OH–M +0.127	OCH_3–П -0.268	OCH_3–O -0.268	OCH_3-M +0.115	
1		–	–	–	–	–	–	–
2		C-3.16	–	–	–	–	–	-0.740
3		–	C-5.18	–	–	–	–	-0.746
4		–	–	–	C-3.16	–	–	-0.536
5		–	–	C-4.17	–	–	–	-0.486
6		C-3.16	–	–	–	–	C-4.17	-0.510
7		–	–	–	C-3.16	–	C-4.17	-0.306
8		C-3.16	–	–	–	–	C-2.15 C-4.17	-0.280
9		–	–	–	C-3.16	–	–	-0.076
10		–	–	–	C-3.16	C-1.14 C-5.18	–	-1.608

Note: * The term “constants” and the values of the σ̄-Taft constants are given in accordance with [24]. They take into account the polar conjugation with the electron-donor reaction center.

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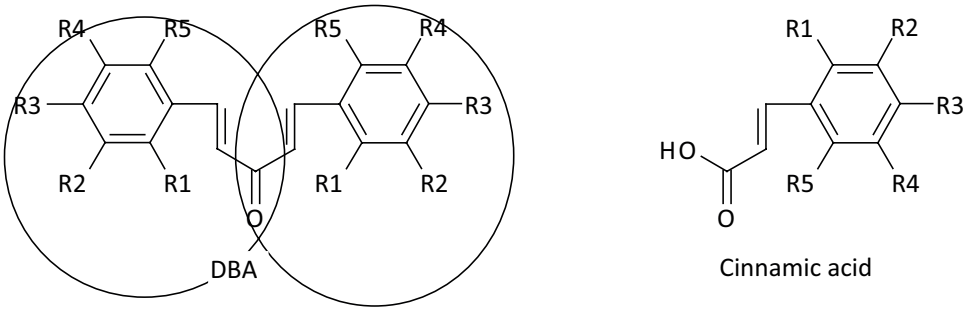

Figure 1 – Structural fragments of dibenzylidenacetone and cinnamic acid
Note: DBA — dibenzylidenacetone.

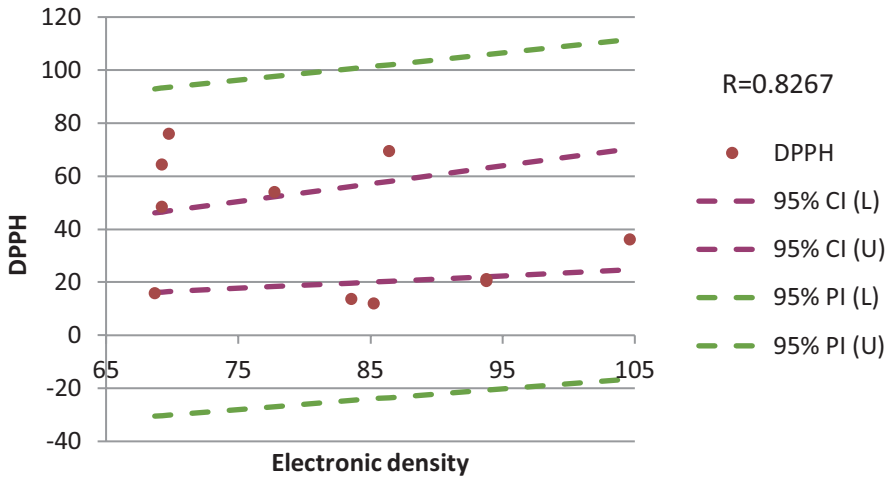

Figure 2 – Correlation relationship between DPPH and electronic density

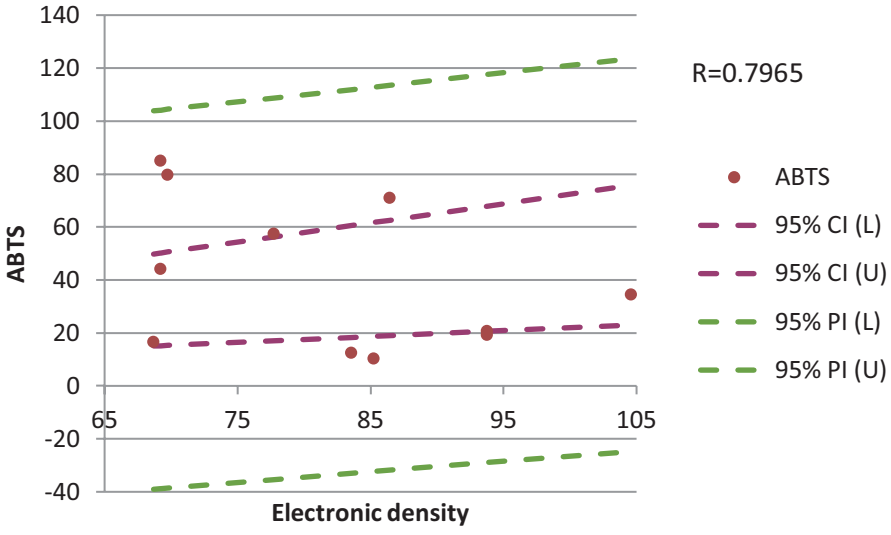

Figure 3 – Correlation relationship between ABTS and electronic density

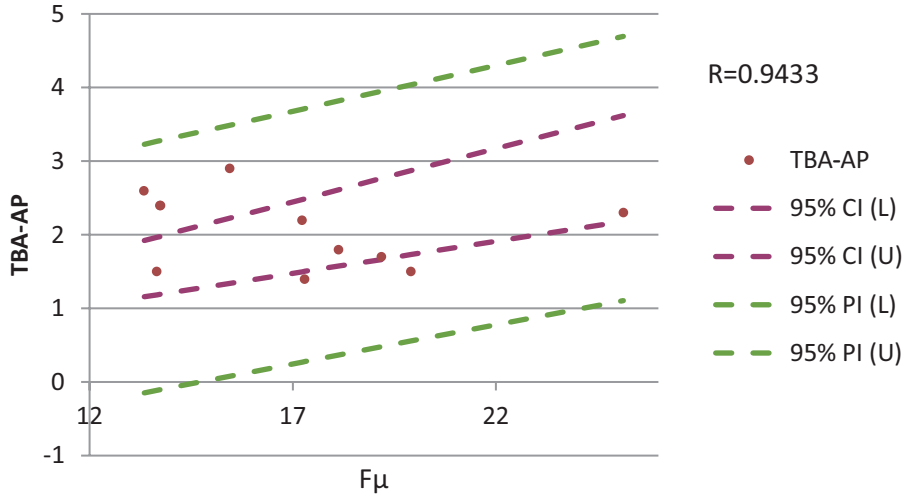

Figure 4 – Correlation relationship between TBA-AP and free valence index

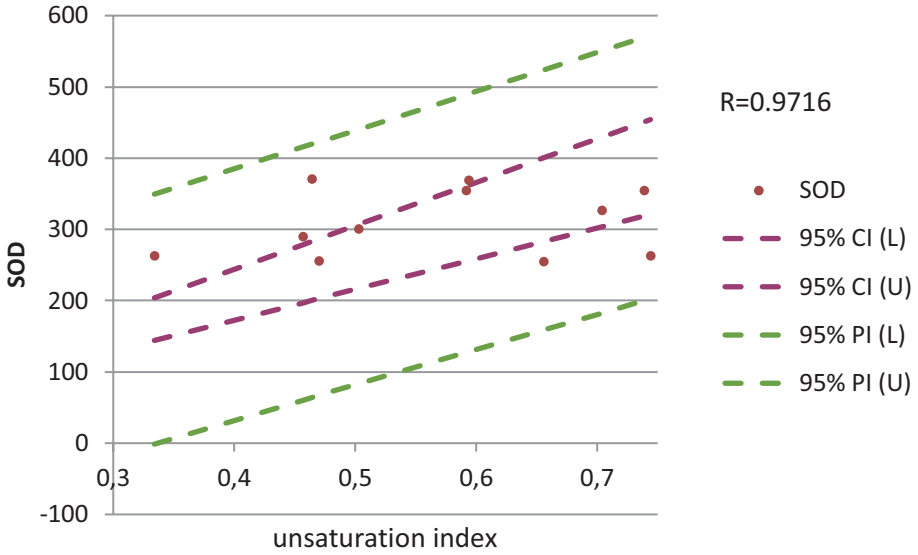

Figure 5 – Correlation between SOD and unsaturation index

When interpreting the biological activity of organic molecules, the problem should be considered taking into account the structural features of the molecules, as well as all physico-chemical parameters, so that the results and conclusions are reliable. So, if the antioxidant activity of the compounds under study is judged only by the IP magnitude, then an error will inevitably arise: compounds 4, 7, 9, and 10 have significantly lower IP values than the most active compounds 5, 6, and 8. In order to avoid such errors, all structural features of the molecules should be taken into account in combination with the other parameters. For example, compounds 4, 7, 9, and 10 lack hydroxy groups in aromatic fragments "A" and "B", and the existing methoxy groups are not able of forming phenoxyl radicals. Compounds 5, 6 and 8, on the contrary, contain free hydroxy groups and, therefore, their antioxidant activity is higher.

Correlation dependencies

In order to identify the relationship between a specific type of activity and the objective parameters of the analyzed molecules, the functional dependences between the level of the antioxidant action and the electron density, the unsaturation index, and the free valence index were determined. The obtained data from the corresponding correlation equations indicate the degree of reliability of the experimental data obtained. Fig. 2–5 show graphs of the functional relationship between the listed quantum chemical parameters and the activity in the corresponding tests.

It should be noted that compounds 4, 7, 9, 10, in which phenolic hydroxy groups are methylated, exhibit their antioxidant activity, in the authors' opinion, only due to the 1,4-diene fragment and therefore, their activity is significantly lower, which is consistent with the previously obtained data for chromone derivatives [25].

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Study limitations

If there are available domestic aldehydes containing, for example, tret-butyl radicals and a hydroxy group between them, it is possible to obtain reliably active antioxidants, the activity of which will be comparable to tocopherols.

CONCLUSION

This article is devoted to the analysis of the quantum chemical parameters of (1E,4E)-1,5-diphenylpent-1,4-diene-3-one derivatives in relation to their antioxidant activity. It has been established that the most informative and reliable are the unsaturation index (IUA), the electron density and the free valence index (Fr). In the experiment using the tests such as DPPH, ABTS, SOD and TBA-AP, it has been found out that the most active compounds are the derivatives containing free hydroxy groups. The most active among them is characterized by the derivative that contains a spatially hindered phenolic hydroxyl, due to which a stable phenoxyl radical is formed. The study of the correlations between the biological activity and quantum chemical parameters indicates that the values of the electron density, free valence indices and unsaturation indices give the most reliable results.

The relationship between the distribution of the electron density on the carbon atoms of the pentadiene fragment and the ionization potential has been shown. The correlation analysis of the functional relationship between the antioxidant activity and IUA, Fr and electron density showed a high reliability of the study data, as evidenced by the correlation coefficients. The authors of the article believe that based on the basic structure of (1E,4E)-1,5-diphenylpent-1,4-diene-3-one, by selecting appropriate substituents in the aromatic fragments, it is possible to significantly increase an antioxidant activity and create pharmacologically promising therapeutic and prophylactic agents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Eduard T. Oganesyan — development of the research concept, preparation of the manuscript;
Victoriya M. Rukovitsina, Simillа L. Adzhiakhmetova — experiment, statistical analysis of the data;
Dmitry I. Pozdnyakov — development of the research concept, experiment, preparation of the manuscript.
All the authors have made equial and equivalent contributions to the preparation of the publication.
All the authors confirm that their authorship meets the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before the publication).

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