DOI: 10.6060/ivkkt.20236609.6906

УДК: 547.497.1

СИНТЕЗ, КОНФОРМАЦИОННЫЙ АНАЛИЗ И АНТИОКИСЛИТЕЛЬНАЯ АКТИВНОСТЬ СЕМИКАРБАЗОНОВ С ФРАГМЕНТАМИ ФЕНОЛА

В.Н. Кошелев, К.В. Ильков, О.В. Примерова, А.А. Гладких

Владимир Николаевич Кошелев (ORCID 0000-0001-5755-5291), Кирилл Владимирович Ильков (ORCID 0000-0001-8961-409X), Ольга Вячеславовна Примерова (ORCID 0000-0002-0162-2528)*, Анастасия Александровна Гладких (ORCID 0009-0006-3781-0666)

Кафедра органической химии и химии нефти, Российский государственный университет нефти и газа им. И.М. Губкина, Ленинский просп., 65, Москва, Российская Федерация, 119991
E-mail: koshelev.v@gubkin.ru, ilkov.k@gubkin.ru, Primerova92@yandex.ru*, anatanielle@yandex.ru

В настоящей работе был синтезирован ряд семикарбазонов, в структуру которых входят фенольные фрагменты, проведен конформационный анализ полученных соединений и оценка их антиокислительных свойств. Семикарбазоны, содержащие фенольные фрагменты, представляют интерес в качестве эффективных антиоксидантов, способных нейтрализовывать свободные радикалы и предотвращать окислительный стресс, который связан с широким спектром хронических заболеваний, включая рак, диабет и сердечно-сосудистые заболевания. Были синтезированы семикарбазоны с фрагментами резорцина, 2-метоксифенола, 2,6-ди-трет-бутилфенола, алкилированного пирокатехина, выходы составили 72-82%. Семикарбазоны 2,3-дигидрокси-4,6-ди-трет-бутилбензальдегида и 4-гидрокси-3,5-ди-трет-бутилацетофенона синтезированы впервые. В ИК спектрах соединений наблюдается поглощение в области 1577–1598 см$^{-1}$, соответствующее частоте валентных колебаний C=N, и сигналы вблизи 1668-1679 см$^{-1}$, соответствующие валентным колебаниям C=O в семикарбазонах. В спектрах ^{1}H ЯМР альдегидные протоны исходных соединений в слабопольной области спектра сменяются острым синглетом при 7,73-9,31 м.д., что свидетельствует о наличии фрагментов CH=N, также присутствует пик в области 10 м.д., соответствующий одному протону NH, и пик на 2 протона при 6 м.д., соответствующий протонам NH_2. Проведен конформационный анализ полученных соединений с помощью квантово-химических расчетов с использованием функционала B3LYP и базисного набора 6-311+G (d,p), а также двумерной корреляционной спектроскопии ЯМР NOESY. Антиоксидантная активность всех продуктов была определена in vitro: активность по удалению катион-радикалов оценивалась с использованием 2,2'-азино-бис(3-этилбензотиазолин-6-сульфоната), а способность восстанавливать железо определялась с использованием метода PFRAP (феррицианида/берлинской лазури). Все исследованные вещества проявили более высокую антиокислительную активность по сравнению с агидолом, лучшую способность ингибировать катион-радикалы показали семикарбазоны с фрагментами 2-метоксифенола и 2,6-ди-трет-бутилфенола, лучшую железовосстанавливающую активность проявили семикарбазоны с фрагментом резорцина и алкилированного пирокатехина.

Ключевые слова: семикарбазоны, фенолы, синтез, антиоксиданты

SYNTHESIS, CONFORMATIONAL ANALYSIS AND ANTIOXIDANT ACTIVITY OF SEMICARBAZONES WITH PHENOL FRAGMENTS

V.N. Koshelev, K.V. Ilkov, O.V. Primerova, A.A. Gladkikh

Vladimir N. Koshelev (ORCID: 0000-0001-5755-5291), Kirill V. Ilkov (ORCID: 0000-0001-8961-409X), Olga V. Primerova (ORCID: 0000-0002-0162-2528)*, Anastasia A. Gladkikh (ORCID: 0009-0006-3781-0666)

Department of Organic Chemistry and Petroleum Chemistry, National University of Oil and Gas «Gubkin University», Leninsky ave., 65, Moscow, 119991, Russia
E-mail: koshelev.v@gubkin.ru, ilkov.k@gubkin.ru, Primerova92@yandex.ru*, anatanielle@yandex.ru

In the present work, a number of semicarbazones with phenolic fragments were synthesized. A conformational analysis of the obtained compounds was carried out, and their antioxidant properties were evaluated. Semicarbazones containing phenolic fragments are of interest as effective antioxidants which are able to neutralize free radicals and prevent oxidative stress, which is associated with a wide range of diseases, including cancer, diabetes, and cardiovascular disease. Semicarbazones with fragments of resorcinol, 2-methoxyphenol, 2,6-di-tert-butylphenol, alkylated pyrocatechol were synthesized. The yields were 72-82%. Semicarbazones of 2,3-dihydroxy-4,6-di-tert-butylbenzaldehyde and 4-hydroxy-3,5-di-tert-butylacetophenone were synthesized for the first time. The IR spectra of the compounds show absorption in the region of 1577–1598 cm^{-1}, corresponding to the frequency of C=N stretching vibrations, and signals near 1668–1679 cm^{-1}, corresponding to C=O stretching vibrations in semicarbazones. In the ^{1}H NMR spectra, the aldehyde protons of the starting compounds in the downfield region of the spectrum are replaced by a sharp singlet at 7.73–9.31 ppm, which indicates the presence of CH=N fragments. There is also a peak in the 10 ppm region corresponding to one NH proton, and peak per 2 protons at 6 ppm corresponding to NH_2 protons. The conformational analysis of the obtained compounds was carried out using quantum chemical calculations using the B3LYP functional and the 6-311+G (d,p) basis set, as well as NOESY two-dimensional NMR correlation spectroscopy. The antioxidant activity of all products was determined in vitro: radical cation scavenging activity was assessed using 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate) and iron reduction capacity was determined using the PFRAP method (ferricyanide/prussian blue). All the studied substances showed a higher antioxidant activity compared to agidol. Semicarbazones with fragments of 2-methoxyphenol and 2,6-di-tert-butylphenol showed the best ability to inhibit radical cations. Semicarbazones with a fragment of resorcinol and alkylated pyrocatechol showed the best iron-reducing activity.

Key words: semicarbazones, phenols, synthesis, antioxidants

Для цитирования:
Кошелев В.Н., Ильков К.В., Примерова О.В., Гладких А.А. Синтез, конформационный анализ и антиокислительная активность семикарбазонов с фрагментами фенола. *Изв. вузов. Химия и хим. технология*. 2023. Т. 66. Вып. 9. С. 71–76. DOI: 10.6060/ivkkt.20236609.6906.

For citation:
Koshelev V.N., Ilkov K.V., Primerova O.V., Gladkikh A.A. Synthesis, conformational analysis and antioxidant activity of semicarbazones with phenol fragments. *ChemChemTech* [*Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.*]. 2023. V. 66. N 9. P. 71–76. DOI: 10.6060/ivkkt.20236609.6906.

INTRODUCTION

Oxidative stress is responsible for a host of cell damage that leads to numerous degenerative diseases, including cancer and cardiovascular disease [1]. Ensuring healthy cellular homeostasis requires the presence of antioxidant enzymes in the body as a protective mechanism or, alternatively, medicinal antioxidants that protect cells from damage caused by free radicals [2]. Antioxidants are compounds that protect cells from damage caused by free radicals, which are unstable molecules produced during normal metabolism and in response to environmental stressors.

Traditionally, compounds containing phenolic fragments in their structure are used as antioxidants. Of great industrial importance are sterically hindered phenols containing either tert-butyl [3] or other bulky substituents in the ortho position to the OH group [4-6].

At the same time, interest in semicarbazones as compounds with antioxidant properties has been growing in recent years [7]. For example, it was shown that semicarbazones can scavenge free radicals and prevent oxidative stress [8], which is associated with a wide range of chronic diseases, including cancer [9], diabetes, and cardiovascular disease [10]. In addition, semicarbazones can be used as compounds with anti-infective activity [11].

It is also important to study the influence of the structure of semicarbazones on their effectiveness as an antioxidant. Significant influence of the complanarity of several conjugated fragments of the molecule for the stabilization of the resulting radicals was noted [12, 13], although in the case of sterically hindered phenols, the complanarity is violated, as shown, for example, in [14]. At the same time, when considering semicarbazones, which also have antioxidant activity, for example, indole-2-carbaldehyde [15], 5-nitrofurfural, and 5-nitrothiophene-2-carbaldehyde [16], it can be noted that they exist as the most stable E-isomers. In [17], the authors studied the effect of the mutual arrangement of the hydroxy groups of the phenol substituent with respect to the semicarbazone fragment, concluding that the ability to intercept radicals deteriorates with an increase in the dissociation energy of the O–H bond due to the possible formation of a hydrogen bond between the hydrogen of the OH group and the nitrogen atom of the imino group. Similar conclusions are reached in the study of cycloaminomethyl derivatives [4], azomethines [18], and sterically hindered dihydroxybenzenes.

EXPERIMENTAL PART

Reagents and solvents were purchased from Acros and Sigma-Aldrich. Melting points were determined using a Stuart SMP30 instrument. IR spectra were recorded using an Agilent Carry 600 spectrometer equipped with an attenuated total reflection (ATR) device. 1H and 13C NMR spectra were recorded at room temperature on a Bruker Avance II 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz); Me_4Si was used as an internal standard. Antioxidant activity was determined using a PB-2201 UV-Vis spectrophotometer.

Synthesis of semicarbazones **1a-e**

The appropriate aldehyde or ketone (10.0 mmol) and semicarbazide hydrochloride (10.0 mmol) were dissolved in ethanol:acetic acid mixture 1:1 (25 ml). Reaction mixture was stirring under reflux for 3-4 h (the reaction was followed by TLC). After that, the reaction mixture was poured into ice water. The precipitate was filtered off and and recrystallized from a suitable solvent.

2,4-Dihydroxybenzaldehyde semicarbazone **1a** Yield 79%, m.p. = 264-266 ℃ (EtOH:H_2O, 2:1).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 s (1H, OH), 8.04 s (1H, CH), 7.50 d (*J* = 9, 1H, H-Ar), 6.32 s (1H, H-Ar), 6.30 d (J = 9, 1H, H-Ar), 5.5 s (2H, NH_2).

^{13}C NMR (75 MHz, DMSO-d_6) δ 160.1, 158.3, 157.9, 157.2, 139.2, 112.5, 107.9, 102.8. FTIR, cm^{-1}, 3475 (OH), 1677 (C=O), 1578 (C=N).

4-Hydroxy-3-methoxybenzaldehyde semicarbazone **1b**. Yield 79%, m.p. 216-218 ℃ (*i*-PrOH).

^{1}H NMR (300 MHz, DMSO-d_6): 10.2 s (1H, OH), 9.31 (1H, CH=N), 7.71 s (1H, H-Ar), 7.35 s (1H, H-Ar), 6.95 d (J = 9, 1H, H-Ar,), 6.74 d (*J* = 9, 1H, H-Ar), 6.49 s (2H, NH_2), 3.78 (c, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6) δ 157.44, 148.42, 148.42, 140.29, 126.75, 121.53, 115.60, 109.32, 56.11. FTIR, cm^{-1}, 3520 (OH), 1698 (C=O), 1642 (C=N).

3,5-di-tert-butyl-4-hydroxybenzaldehyde semicarbazone **1c**. Yield 72%. m.p. 192-194 ℃ (EtOH:H_2O, 3:1).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 s (1H, NH), 7.73 s (1H, CH=N), 7.34 s (2H, H-Ar), 7.23 s (1H, OH), 6.35 s (2H, NH_2), 1.38 s (18H, t-Bu).

^{13}C NMR (75 MHz, DMSO-d_6) δ 157.31, 155.68, 141.42, 139.62, 126.46, 123.67, 34.98, 30.71. FTIR, cm^{-1}, 3622 (OH), 1679 (C=O), 1569 (C=N).

4,6-di-tert-butyl-2,3-dihydroxybenzaldehyde semicarbazone **1d** Yield 82%, m.p. 213-214℃ (EtOH:H_2O, 2:1).

^{1}H NMR (600 MHz, DMSO-d_6) δ 12.01 s (1H, OH), 10.46 s (1H, NH), 8.78 s (1H, OH), 8.08 s (1H, CH=N), 6.74 s (1H, H-Ar), 6.26 s (2H, NH_2), 1.37 (c, 9H, t-Bu), 1.35 s (9H, t-Bu)

^{13}C NMR (75 MHz, DMSO-d_6) δ 155.82, 147.10, 143.93, 142.46, 138.20, 135.10, 114.32, 113.90, 35.49, 35.17, 32.83, 29.68. FTIR, cm^{-1}, 3502 (OH), 3389 (OH), 1668 (C=O), 1584 (C=N).

3,5-Di-tert-butyl-4-hydroxyacetophenone semicarbazone **1e**. Yield 75%. m.p. 212-214 ℃ (EtOH:H_2O, 1:1).

^{1}H ЯМР (600 MHz, $CDCl_3$): δ 8.69 s (1H, NH), 7.53 s (2H, H-Ar), 5.43 s (1H, OH), 2.27 s (3H, CH_3), 1.49 s (18H, t-Bu).

^{13}C ЯМР (151 MHz, $CDCl_3$): δ 158.33, 154.98, 147.31, 135.88, 129.60, 123.05, 34.42, 30.23. FTIR, $см^{-1}$, 3548 (OH), 1662 (C=O), 1598 (C=N).

Antioxidant activity

ABTS assay 2,2’-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (Sigma) radical cation (ABTS$^{+\cdot}$) was produced by reacting 7 mM ABTS water solution with 2.45 mM potassium persulfate and allowing the mixture to stand in the dark at room temperature for 12-16 h before use. A dark blue color should be developed. The working solution was prepared by taking a volume of the previous solution and diluting it in ethanol until its absorbance was 0.70 ± 0.02 at 734 nm. To 2.7 ml of working solutions 300 μl of 1 mmol solution of prepared compounds in DMSO were added. After 10 min the absorbance at 734 nm was measured using a spectrofotometer. The percentage inhibition calculated as ABTS radical scavenging activity (%) = (Abscontrol−Abssample)/Abscontrol where Abscontrol is the absorbance of ABTS radical in methanol; Abssample is the absorbance of ABTS radical solution mixed with sample extract/standard. All determinations were performed in triplicate.

Ferric ion-reducing capacity assay. Sample solutions were prepared in 50 mM phosphate buffer, pH 7.0 and 500 μL of dilutions were mixed with 250 μL of 1% potassium ferricyanide solution followed by incubation for 20 min at 50 °C. After the incubation 500 μL of 10% trichloroacetic acid was mixed with 500 μL of the incubated sample, 100 μL of 0.1% ferric chloride and 500 μL of distilled water. The mixture was left to incubate for 10 min at room temperature and the absorbance was immediately measured at 700 nm, against blank, which consisted of phosphate buffer and appropriate volume of solvent. The results were expressed as absorbance units at 700 nm which was considered as a measure of reducing power.

Calculations

Quantum-chemical calculations were performed using the Gaussian09 program [19]; the results were visualized with GaussView 6.0.16. All calculations were performed with the B3LYP functional using the 6-311+G (d,p) basis, since it was previously shown [20] that this method gives the most accurate results.

RESULTS AND DISCUSSIONS

A number of semicarbazones were synthesized during the condensation of semicarbazide and a number of aldehydes: formylresorcinol, vanillin, 4,6-di-tert-butyl-2,3-dihydroxybenzaldehyde, 3,5-di-tert-butyl-4-hydroxybenzaldehyde, and 3,5-di-tert-butyl-4-hydroxyacetophenone (fig. 1). The reaction was carried out by reflux the initial reagents in a mixture of ethanol and acetic acid in a ratio of 1:1. The yields of target semicarbazones were 72-82%. The cH-Aracteristics and spectral data of compounds **1a-c** correspond to the literature data; compounds **1d** and **1e** were synthesized for the first time. The IR spectra of compounds **1a-1e** show absorption in the region of 1577-1598 cm^{-1}, corresponding to the frequency of C=N stretching vibrations, and signals near 1668-1679 cm^{-1}, corresponding to C=O stretching vibrations in semicarbazones [21]. The ^{1}H NMR spectrum of compound **1d** is cH-Aracteristic of compounds **1a-1d**: aldehyde protons of the initial compound at 10.08 ppm. are replaced by a sH-Arp singlet at 8.36 ppm, which indicates the presence of a CH=N fragment, there is also a peak at 10.46 ppm, corresponding to one NH proton, and a peak for 2 protons at 6.26 ppm, corresponding to NH$_2$ protons.

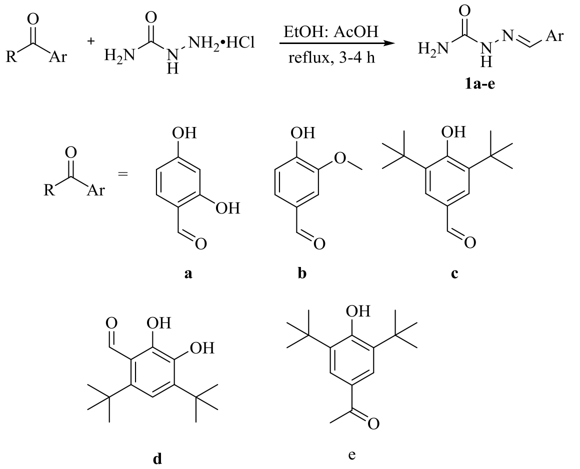
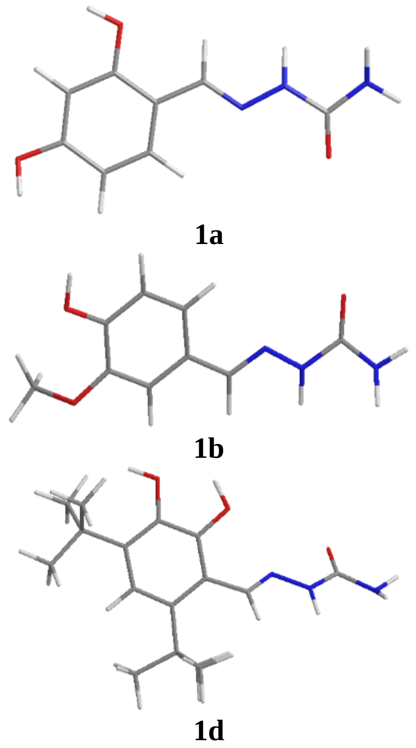


Fig. 1. Scheme of the synthesis of semicarbazones
Рис. 1. Схема синтеза семикарбазонов

To reveal the predominance of one particular conformer, a PES scan was performed with the theoretical approximation B3LYP/6–311+G (D, P). To determine the lowest energy conformation of the compounds, the torsion angle H5-C5-C6-C7 (φ) associated with the coordinates of the conformational flexibility of the compounds was investigated. This angle was rotated between 0° and 180°, in 5° increments. The structures of the lowest energy isomers are shown in fig. 2, the results of the PES scan of the compounds are shown in fig. 3.



1a

1b

1d

Fig. 2. Structures of the most stable conformations of semicarbazones **1a**, **1b**, and **1d**
Рис. 2. Наиболее устойчивые конформации семикарбазонов **1a**, **1b** и **1d**

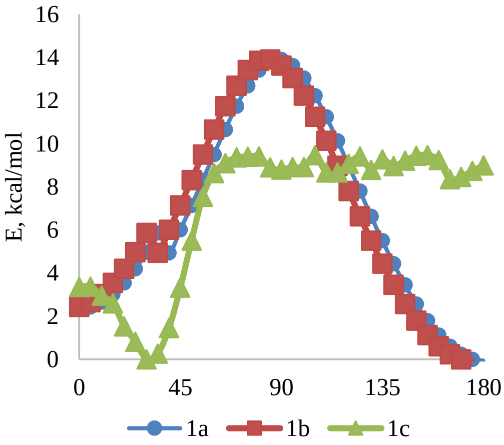
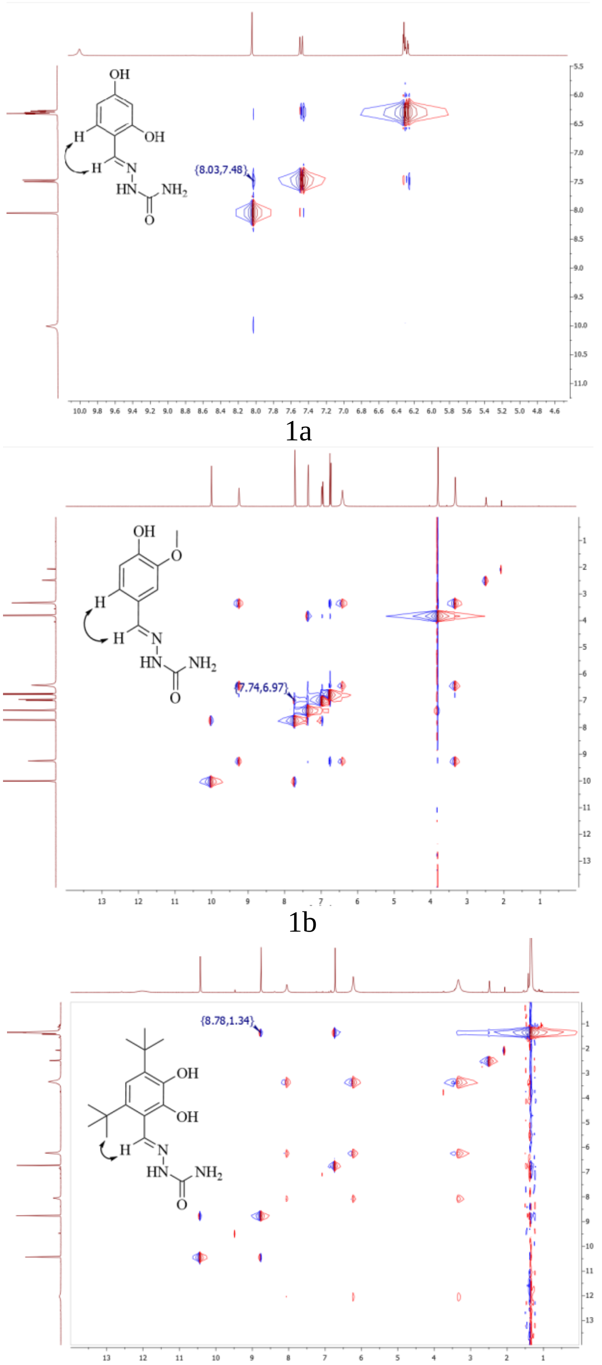


Рис. 3. Конформационный анализ семикарбазонов **1a**, **1b** и **1d**
Fig. 3. PES analysis of semicarbazones **1a**, **1b**, and **1d**

It was noted that for formylresorcinol semicarbazones **1a** and vanillin **1b**, the Z-isomer is more stable, which can be concern with formation of hydrogen bond O---H-C. For **1d**, there is a strong spatial interaction of both the phenolic OH group and the tert-butyl group with the hydrogen atom at the double bond; the most stable rotamer has a value of φ 30°.

To correlate the predicted energy values with the structure, the 2D-NOESY spectra were analyzed; fig. 4 shows the spectra of compounds **1a**, **1b** and **1d**.



1a

1b

1d

Fig. 4. NOESY spectra of semicarbazones **1a**, **1b**, and **1d**
Рис. 4. Спектры NOESY семикарбазонов **1a**, **1b**, **1d**

In the spectrum of compound **1a** there is a cross peak of the proton of the azomethine group and the proton of the aromatic ring. The spectrum of semicarbazone **1b** showed a correlation between the proton of the CH=N group and the aromatic doublet. In the spectrum of compound **1d**, there is a correlation between the CH proton of the azomethine group (8.78 ppm) and the protons of the tert-butyl group (1.34 ppm) and no correlation between the CH and OH protons. The obtained data confirm the conformer structures shown in fig. 2.

The antioxidant activity of the synthesized compounds was studied by two methods: the ability to scavenge radical cations was analyzed by the ABTS method, and the electron donor ability by the PFRAP method [22]. 4-Methyl-2,6-di-tert-butylphenol (Agidol) was used as a standard.

Table 1

Antioxidant activity of semicarbazones
Таблица. Антиокислительная активность семикарбазонов

	Efficiency ABTS$^{\cdot+}$, %	PFRAP, absorbanse
Agidol	35.67	0.148
1a	43.74	0.3
1b	74.37	0.125
1c	70.38	0.115
1d	41.75	0.293
1e	45.26	0.225

According to the results of tests by the ABTS method, vanillin semicarbazones **1b** and 3,5-di-tert-butyl4-hydroxybenzaldehyde **1c** showed the best results, semicarbazones **1a** and **1d**, in which the azomethine group is in the ortho-position to the hydroxyl group, showed less activity. Compounds **1c** and **1e**, which contain 2,6-di-tert-butylphenol, differ significantly in the efficiency of inhibition of radical cations; aldehyde-based semicarbazone showed significantly higher activity than ketone-based semicarbazone. Semicarbazones with resorcinol fragment **1a** and alkylated pyrocatechol **1d** showed the best iron-reducing activity; semicarbazone based on ketone **1e** also showed high efficiency.

CONCLUSIONS

A number of semicarbazones with phenol fragments were synthesized in good yields, including 4,6-di-tert-butyl-2,3-dihydroxybenzaldehyde and 3,5-di-tert-butyl-4-hydroxy-acetophenone semicarbazones, which were not previously described in the literature. Conformational analysis of the obtained substances showed that the compounds are mostly have Z-configuration. All the studied substances showed a higher ability to inhibit radical cations compared to agidol, semicarbazones with fragments of 2-methoxyphenol and 2,6-di-tert-butylphenol showed the best activity, semicarbazones with a fragment of resorcinol and alkylated pyrocatechol showed the best iron-reducing activity.

The authors declare the absence a conflict of interest warranting disclosure in this article.

Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.

REFERENCES
ЛИТЕРАТУРА

1. **Pisoschi A.M., Pop A., Iordache F., Stanca L., Predoi G., Serban A.I.** // *Eur. J. Med. Chem.* 2021. V. 209. P. 112891. DOI: 10.1016/j.ejmech.2020.112891.
2. **Halliwell B.** How to characterize an antioxidant: an update. Biochemical Society Symposium. 1995. 61. P. 73–101. DOI: 10.1042/bss0610073.
3. **Li J., Zhang S., Kuang Y., Bi Y., Wang H.** // *J. Am. Oil Chem. Soc.* 2023. V. 100. N 4. P. 259-285. DOI: 10.1002/aocs.12684.
4. **Ksendzova G.A., Ostrovskaya N.I., Sorokin V.L., Shadyro O.I.** // *High Energy Chemistry*. 2022. V. 56. N 5. P. 344-347. DOI: 10.1134/S0018143922050083.
5. **Нагиева М.В., Расулов Ч.К.** // *Изв. вузов. Химия и хим. технология.* 2023. Т. 66. Вып. 6. С. 85-93. DOI: 10.6060/ivkkt.20236606.6777.
   Nagieva M.V., Rasulov Ch.K. *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.]*. 2023. V. 66. N. 6. P. 85-93 (in Russian). DOI: 10.6060/ivkkt.20236606.6777.
6. **Агамалиев З.З., Аббасов В.М., Расулов Ч.К., Назаров И.Г., Рзаева Н.Ш., Нагиева М.В.**// *Изв. вузов. Химия и хим. технология.* 2019. Т. 62. Вып. 2. С. 17-24. DOI: 10.6060/ivkkt.20196202.5786.
   Agamaliev Z.Z.., Abbasov V.M., Rasulov Ch.K., Nazarov I.G., Rzaeva N.Sh., Nagieva M.V. *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.].* 2019. V. 62. N 2. P. 17-24 (in Russian). DOI: 10.6060/ivkkt.20196202.5786.
7. **Nagamallu R., Srinivasan B., Ningappa M.B., Kariyappa A.K.** // *Bioorg. Med. Chem. Lett.* 2016. V. 26. N 2. P. 690-694. DOI: 10.1016/j.bmcl.2015.11.038.
8. **Dutta S., Padhye S., Priyadarsini K.I., Newton C.** // *Bioorg. Med. Chem. Lett.* 2005. V. 15. N 11. P. 2738-2744. DOI: 10.1016/j.bmcl.2005.04.001.
9. **More M.S., Joshi P.G., Mishra Y.K., Khanna P.K.** // *Mater. Today Chem.* 2019. V. 14. P. 100195. DOI: 10.1016/j.mtchem.2019.100195.
10. **Laufer S.A., Striegel H.-G., Wagner G.K.** // *J. Med. Chem.* 2002. V. 45. N 21. P. 4695-4705. DOI: 10.1021/jm020873z.
11. **Scarim C.B., Jornada D.H., Machado M.G.M., Ferreira C.M.R., dos Santos J.L., Chung M.C.** // *Eur. J. Med. Chem.* 2019. V. 162. P. 378-395. DOI: 10.1016/j.ejmech.2018.11.013.
12. **Nakayama T., Uno B.** // *J. Agricult. Food Chem.* 2023. V. 71. N 10. P. 4382-4393. DOI: 10.1021/acs.jafc.2c08105.
13. **Shi G., Gu L., Jung H., Chung W.-J., Koo S.** // *ACS Omega.* 2021. V. 6. N 38. P. 25096-25108. DOI: 10.1021/acsomega.1c04432.
14. **Тухватуллин Р.Ф., Колчина Г.Ю., Мовсумзаде Э.М., Мамедова П.Ш., Бабаев Э.Р.** // *Изв. вузов. Химия и хим. технология.* 2018. Т. 61. Вып. 4-5. С. 84-92. DOI: 10.6060/tcct.20186104-05.5659.
    Tukhvatullin R.F., Kolchina G.Yu., Movsumzade E.V., Mamedova P.Sh. Babaev E.R. // *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.].* 2018. V. 61. N 4-5. P. 84-92 (in Russian). DOI: 10.6060/tcct.20186104-05.5659.
15. **Carrasco F., Hernández W., Chupayo O., Álvarez C.M., Oramas-Royo S., Spodine E., Tamariz-Angeles C., Olivera-Gonzales P., Dávalos J.Z.** // *J. Chem.* 2020. V. 2020. P. 7157281. DOI: 10.1155/2020/7157281.
16. **Cerecetto H., Di Maio R., González M., Risso M., Sagrera G., Seoane G., Denicola A., Peluffo G., Quijano C., Stoppani A.O.M., Paulino M., Olea-Azar C., Basombrío M.A.** // *Eur. J. Med. Chem.* 2000. V. 35. N 3. P. 343-350. DOI: 10.1016/S0223-5234(00)00131-8.
17. **Nath A.R., Yehye W.A., Johan M.R.B.** // *J. Therm. Anal. Calorim.* 2021. V. 146. N 5. P. 2101-2114. DOI: 10.1007/s10973-020-10199-8.
18. **Ksendzova G.A., Ostrovskaya N.I., Semenkova G.N., Sorokin V.L., Shishkanova P.A., Shadyro O.I.** // *Russ. J. Gen. Chem.* 2019. V. 89. N 3. P. 391-398. DOI: 10.1134/S1070363219030046.
19. **Dennington R., Keith T., Millam J.** Semichem Inc. Shawnee Mission KS, GaussView, Version. 2009. V. 5. N 8.
20. **Venkatachalam T., Pierens G.K., Reutens D.C.** // *Magn. Reson. Chem.* 2014. V. 52. N 3. P. 98-105. DOI: 10.1002/mrc.4041.
21. **Pretsch E., Bühlmann P., Affolter C., Pretsch E., Bhuhlmann P., Affolter C.** Structure determination of organic compounds. Springer. 2000. DOI: 10.1007/978-3-662-04201-4.
22. **Jakovljević K., Matić I.Z., Stanojković T., Krivokuća A., Marković V., Joksović M.D., Mihailović N., Nićiforović M., Joksović L.** // *Bioorg. Med. Chem. Lett.* 2017. V. 27. N 16. P. 3709-3715. DOI: 10.1016/j.bmcl.2017.07.003.

Поступила в редакцию 22.05.2023
Принята к опубликованию 30.05.2023

Received 22.05.2023
Accepted 30.05.2023