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SYNTHESIS, ANTIOXIDANT ACTIVITY AND ADME ANALYSIS OF SOME N^4-SUBSTITUTED THIOSEMICARBAZONES WITH β–IONONE FRAGMENT

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Thiosemicarbazones are organic compounds with remarkable biological properties, including anticancer, antibiotic, antifungal, and antioxidant effects. Some of these compounds have found application in medicine and are currently in use or undergoing clinical trials. One of the key problems in the application of chemical compounds, including thiosemicarbazones, in medical practice is their toxicity. A possible solution to this problem may be the synthesis of thiosemicarbazones based on natural fragments. This may lead to improved biological properties and reduced toxicity. In this work, four thiosemicarbazones were synthesized based on β-ionone. DPPH radical inhibition analysis was performed to reveal the antioxidant potential of the synthesized compounds. In addition, ADME (abbreviation (acronym) for absorption, distribution, metabolism, and excretion) screening was performed to identify some pharmacological parameters, which are essential for the potential use of the compound in the medicinal field.

Keywords*: thiosemicarbazones, antioxidant activity, DPPH, β-ionone, ADME screening*

SINTEZA, ACTIVITATE ANTIOXIDANTĂ ȘI MODELAREA ADME A UNOR TIOSEMICARBAZONE N^4-SUBSTITUITE CU FRAGMENT DE β-IONONĂ

Tiosemicarbazonele sunt compuși organici cu efecte biologice remarcabile, printre care se regăsesc efectele anticancer, antibiotice, antifungice și antioxidative. Unii din acești compuși și-au găsit aplicare în medicină și sunt utilizați curent sau trec testările clinice. Una dintre problemele esențiale în aplicarea compușilor chimici, inclusiv a tiosemicarbazonelor, în practica medicinală este toxicitatea lor. O soluție posibilă a acestei probleme poate servi sinteza tiosemicarbazonelor în baza fragmentelor compușilor naturali ce poate contribui la îmbunătățirea proprietăților biologice și la scăderea toxicității. În această lucrare, sunt prezentate rezultatele sintezei a patru tiosemicarbazone în baza β-iononei. Determinarea acțiunii antioxidante *in vitro* la inhibarea radicalului 2,2-difenil-1-picrilhidrazil (DPPH) a fost efectuată pentru identificarea potențialului terapeutic antioxidativ al compușilor sintetizați. Pentru determinarea proprietăților fundamentale în dezvoltarea terapeutică, a fost efectuat screening-ul ADME (abreviere: absorbția, distribuția, metabolizarea și eliminarea) pentru identificarea parametrilor farmacologici esențiali la utilizarea potențială a compusului în domeniu medicinal.

Cuvinte-cheie: *tiosemicarbazone, activitatea antioxidantă, DPPH, β-iononă, modelare ADME.*

INTRODUCTION

In recent decades, cancer has remained one of the leading causes of death worldwide [1] (figure 1), being not only a medical but also a serious socio-economic problem. According to the World Health Organization, millions of new cases of malignant neoplasms are registered annually, and forecasts indicate a further increase in incidence. Despite significant advances in diagnosis and therapy, modern treatment methods are often accompanied by pronounced side effects and do not always ensure a complete cure. In this regard, the search for new approaches to the prevention and treatment of cancer remains one of the priority tasks of modern science.

One of the key factors involved in the initiation and progression of tumor processes is oxidative stress—an imbalance between the formation of reactive oxygen species (ROS) and the ability of cellular antioxidant systems to neutralize their effects [2]. Excessive accumulation of ROS leads to damage to biomolecules, including lipids, proteins, and nucleic acids, which in turn contributes to mutagenesis, inflammatory processes, and the activation of signalling pathways associated with carcinogenesis [3-4]. Thus, restoring redox balance and reducing oxidative stress are considered promising directions for cancer prevention and therapy.

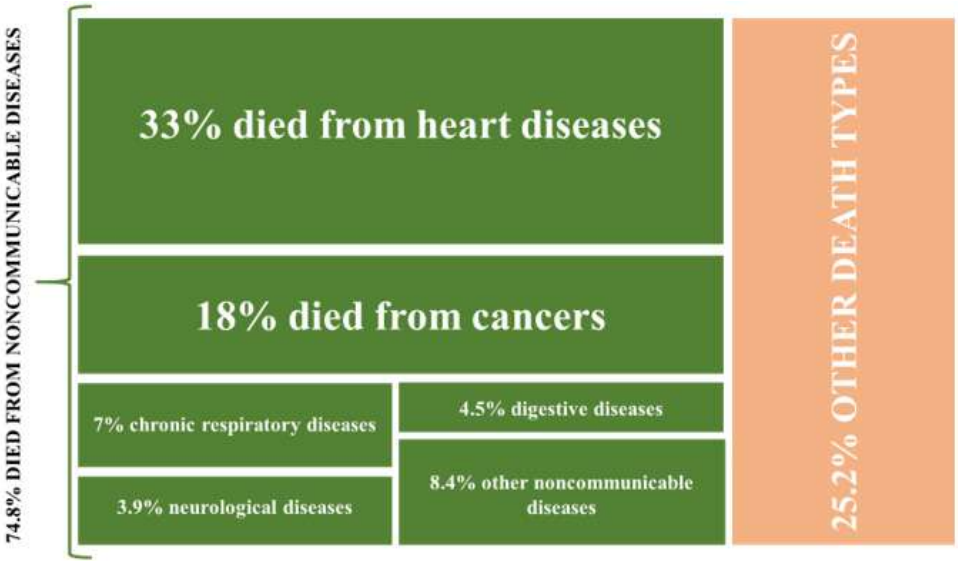


Figure 1. Global causes of death, 2019 [1].

In recent years, increasing attention has been devoted to the search for new synthetic and natural compounds with pronounced antioxidant activity. Among such compounds, thiosemicarbazones have attracted significant interest due to their remarkable structural diversity and broad spectrum of biological properties. Numerous research groups have focused on their synthesis and biological evaluation. Thiosemicarbazones are known for their antimicrobial [5-7], antifungal [7-9], antiviral [10], anticancer [11-14], antioxidant [15-18] and anti-inflammatory [19] activities. Their biological potential is well recognized in pharmacology, with compound such as Triapine serves as notable example [20].

In addition, a large number of thiosemicarbazones incorporating natural fragments have been synthesized [21-24]. These hybrid molecules have demonstrated promising results in various biological assays [21-24]. The inclusion of natural moieties can also reduce the toxicity of thiosemicarbazones, addressing one of the key limitations hindering their clinical application. Furthermore, the functionalization of naturally active compounds may lead to an enhancement of their pharmacological properties.

β-Ionone (4-[2,6,6-trimethyl-1-cyclohexen-1-yl]-3-buten-2-one), is a cyclic terpenoid compound that forms the core structure of retinol, β-carotene and vitamin A (see figure 2) [25]. This volatile aromatic compound has been isolated from plant oils, such as *Viola odorata, Boronia megastigma Nees, Petunia hybrida, Cistus monspeliensis, Lepidium meyenii, Medicago marina, Osmanthus fragrans, Rosa bourboniana, Thymus serpyllum* and other species [25].

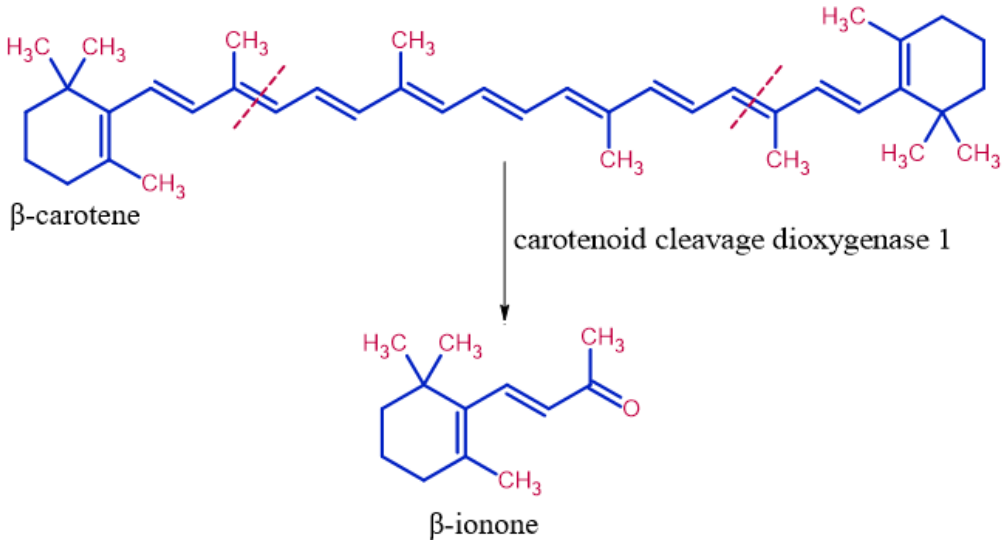


Figure 2. Production of β-ionone from β-carotene by carotenoid cleavage dioxygenase 1 (CCD1) [25].

β-Ionone also can be found in fruits, vegetables and cereals that contain β-carotene, such as carrots, raspberries, roasted almonds, tea and tomatoes [25]. Additionally, β-Ionone is a component that is used in perfumery, decorative cosmetics, fine fragrances [26], shampoos, soaps and other products, so it's considered an important flavour contributor.

Studies have demonstrated that β-ionone and its derivatives may exhibit significant pharmacologic activities, such as antileishmanial [27], anti-inflammatory [28] and antimicrobial [29] activities.

Taking into consideration written above, there is a perspective of synthesizing new thiosemicarbazones based on β-ionone. These have good potential to exhibit useful biological activities, having lower toxicity. In this article the synthesis, physicochemical research, antioxidant activity analysis and *in silico* investigation of some thiosemicarbazones based on β-ionone are described.

MATERIALS AND METHODS

Synthesis of precursors

Phenyl isothiocyanate

In a round bottom flask, a mixture of 1 equivalent of aniline and isopropanol was placed. Then 1 equivalent of tetramethylthiuram disulfide (TMTD) was added and the obtained mixture was refluxed for 3 hours. The end of the reaction was determined by thin layer chromatography. The mixture was cooled to the room temperature and then added to the ice-water mixture. The precipitated solid was filtered and dissolved in a minimal amount of concentrated hydrochloric acid. The resulting solution was filtered form elemental sulphur and then diluted with distilled water until the white solid precipitated. The obtained solid was recrystallized from ethanol to yield white crystalline solid of compound **(1)**.

Then, in a round bottom flask, 1 equivalent of compound **(1)** was mixed with toluene and 1 equivalent of acetic anhydride. Resulted mixture was refluxed for 2 hours. Then it was cooled to the room temperature and washed three times with water. Toluene layer was separated and dried over anhydrous Na_2SO_4. The toluene was distilled off to result a yellowish oil of phenyl isothiocyanate (compound **2**).

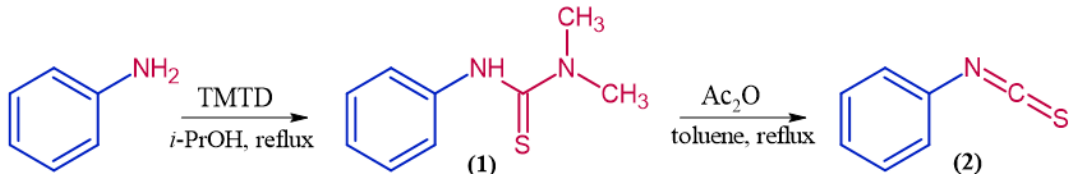


Figure 3. Synthesis scheme of the phenyl isothiocyanate.

General procedure of thiosemicarbazides synthesis

In a round bottom flask, hydrazine monohydrate 1 equivalent was dissolved in tetrahydrofuran. Then to the obtained mixture 1 equivalent of corresponding isothiocyanate solution in tetrahydrofuran, was added dropwise. After complete addition of isothiocyanate solution, mixture was stirred for half an hour more. Precipitated solid was filtered and washed with ice-cold tetrahydrofuran and water and then recrystallized from ethanol-tetrahydrofuran to yield white crystalline solid of corresponding thiosemicarbazide.

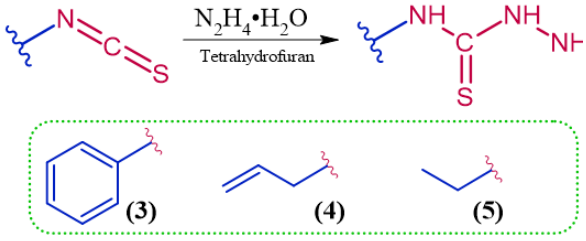


Figure 4. General synthesis scheme of the thiosemicarbazides 3-5.

General synthesis procedure of thiosemicarbazones

In a round bottom flask, 1 equivalent of β-ionone and 1 equivalent of corresponding thiosemicarbazide were mixed. Ethanol and 0.5 mL of hydrochloric acid was added and then mixture was refluxed for 1-4

hours. Then, reaction solution was concentrated by rotary evaporator and left overnight to result yellow crystalline solids.

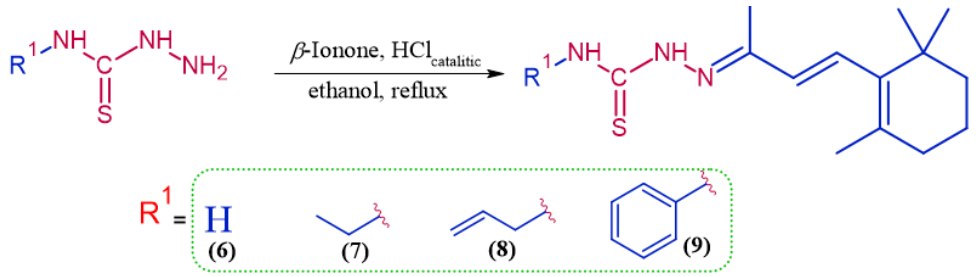


Figure 5. General synthesis scheme of the thiosemicarbazones 6-9.

Antioxidant analysis by DPPH method

For the free radical scavenging activity analysis by the DPPH method, the procedure described in [30] was repeated without any modifications.

ADME analysis

ADME analysis was performed using SwissADME [31]. For this purpose, SMILES code was generated for each investigated thiosemicarbazone.

RESULTS AND DISCUSIONS

Synthesised compounds

In total 4 thiosemicarbazones of β -ionone with different substituents at the N^4 position were synthesized. Their structure was confirmed by NMR spectroscopy. In addition, their antioxidant activity and ADME profile were also investigated. The figure 6 shows the structure of the synthesized compounds.

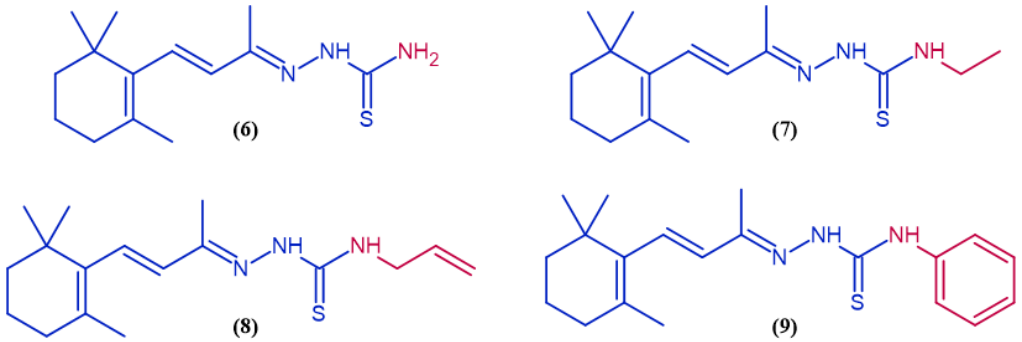


Figure 6. Structure of the synthesised thiosemicarbazones.

β-ionone thiosemicarbazone **(6)**

Yellow crystalline solid, yield 87%. **^{1}H NMR** (DMSO-d_6; δ, ppm): 1.02 (s, 6H); 1.44 (m, 2H); 1.57 (m, 2H); 1.68 (s, 3H); 2.01 (m, 2H); 2.05 (s, 3H); 6.11 (d, 1H); 6.58 (d, 1H); 7.74 (s, 1H); 8.17 (s, 1H). **^{13}C NMR** (DMSO-d_6; δ, ppm): 11.83; 18.62; 21.42; 28.68; 32.54; 33.76; 130.45; 132.36; 133.06; 136.64; 149.1; 178.53.

β-ionone 4-ethylthiosemicarbazone **(7)**

Yellow solid, yield 78%. **^{1}H NMR** (DMSO-d_6; δ, ppm): 1.02 (s, 6H); 1.11 (t, 3H); 1.44 (m, 2H); 1.57 (m, 2H); 1.69 (s, 3H); 2.03 (m, 5H); 3.55 (m, 2H); 6.14 (d, 1H); 6.57 (d, 1H); 8.38 (t, 1H); 10.08 (s, 1H). **^{13}C NMR** (DMSO-*d6*; δ, ppm): 11.73; 14.54; 18.63; 21.43; 28.67; 32.51; 33.77; 38.24; 130.35; 132.24; 133.07; 136.69; 148.76; 177.24.

β-ionone 4-allylthiosemicarbazone **(8)**

Yellow solid, total yield 84%. **^{1}H NMR** (DMSO-d_6; δ, ppm): 1.02 (s, 6H); 1.44 (m, 2H); 1.57 (m, 2H); 1.69 (s, 3H); 2.01 (t, 2H); 2.07 (s, 3H); 4.18 (m, 2H), 5.07-5.12 (m, 2H); 5.88 (m, 1H); 6.15 (d, 1H); 6.58 (d, 1H); 8.50 (t, 1H); 10.23 (s, 1H). **^{13}C NMR** (DMSO-d_6; δ, ppm): 11.84; 18.62; 21.44; 28.69; 32.53; 33.77; 45.74; 115.61; 130.46; 132.38; 133.02; 134.95; 136.67; 149.07; 177.77.

β-ionone 4-phenylthiosemicarbazone **(9)**

Yellow solid, total yield 81%. **^{1}H NMR** (DMSO-d_6; δ, ppm): 1.04 (s 6H); 1.45 (m 2H); 1.58 (m, 2H); 1.72 (s, 3H); 2.02 (m, 2H); 2.13 (s, 3H); 6.28 (d, 1H); 6.63 (d, 1H); 7.17 (m, 1H); 7.27-7.35 (m, 4H); 10.03 (s, 1H); 10.56 (s, 1H). **^{13}C NMR** (DMSO-d_6; δ, ppm): 12.06; 18.66; 21.51; 28.57; 28.74; 32.61; 33.83; 123.54; 125.12; 128.05; 130.71; 132.94; 133.05; 136.74; 139.04; 149.84; 176.33.

NMR spectroscopy

The figure 7 demonstrates the ^{1}H-NMR spectrum of compound **8** - β-ionone 4-allylthiosemicarbazone. At 10.23 ppm, there is a singlet peak characteristic for hydrogen bonded to nitrogen adjacent to the azomethine group. This signal is a characteristic for all thiosemicarbazones and is present in the spectra of all synthesized thiosemicarbazones. The methyl groups from the β-ionone moiety are found at 1.02 and 1.69 ppm, while the CH_2 groups from the β-ionone ring are found in the range between 2.01 and 1.44 ppm. The hydrogens of the olefin group of β-ionone are found at 6.15 and 6.58 ppm in the form of doublets.

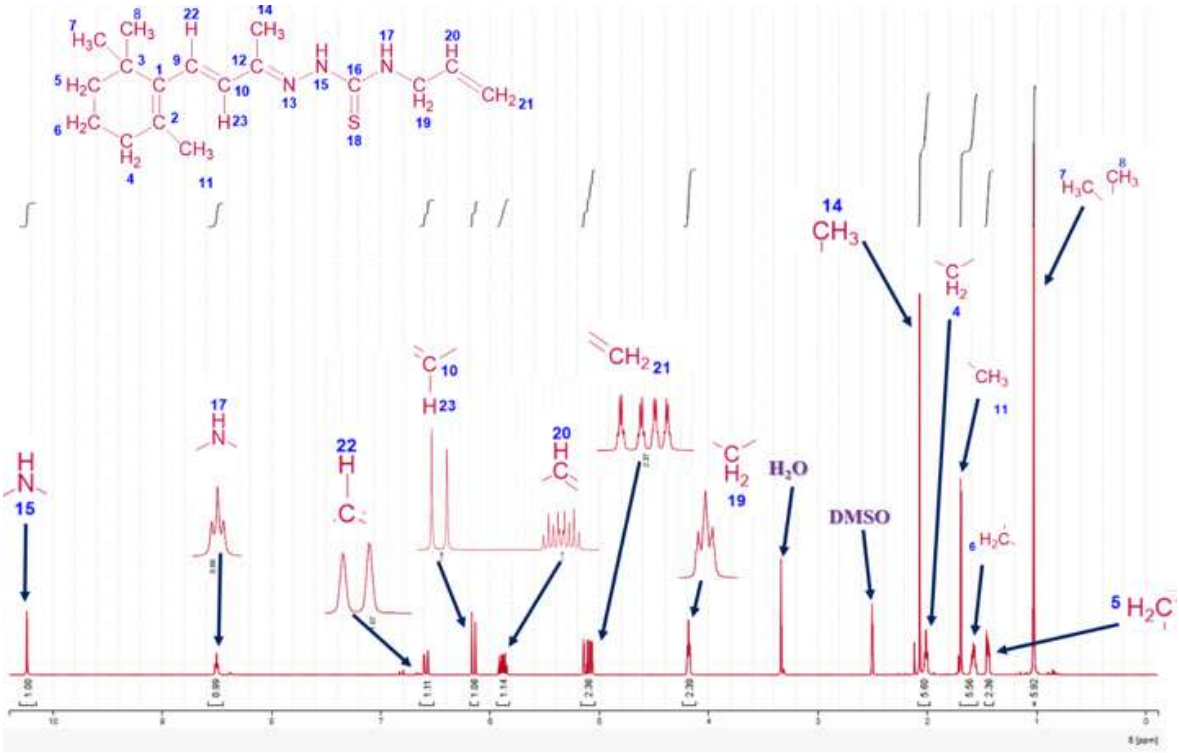


Figure 7. The ^{1}H-NMR spectrum of the thiosemicarbazone 8.

ADME analysis

The ADME (Adsorption Distribution Metabolism Excretion) study is an essential tool in the synthesis of biologically active compounds with potential for application in the pharmaceutical field. It allows initial evaluation of parameters and properties that are crucial for a future drug. In addition, ADME screening allows researchers to understand whether the synthesized compound fits into established theoretical pharmaceutical models and to formulate conclusions about the potential, shortcomings, and risks associated with the synthesized compounds.

On the figure 8 the structural formulas of the synthesized compounds and diagrams with six pharmacologically important properties are demonstrated. The LIPO parameter stands for lipophilicity, which is characterized by the octanol-water partition coefficient. It is considered that the optimal values for a biologically active compound should be between -0.5 and 5. Compounds which are too polar cannot pass through the cell membrane, while substances that are too lipophilic remain in the membrane. For these reasons, in order for a compound to exhibit the desired biological activity, it must have an optimal partition coefficient value, neither too high nor too low. The partition coefficient (logP) values calculated for all compounds are presented in Table 1. It is clear that all compounds have optimal values for this index.

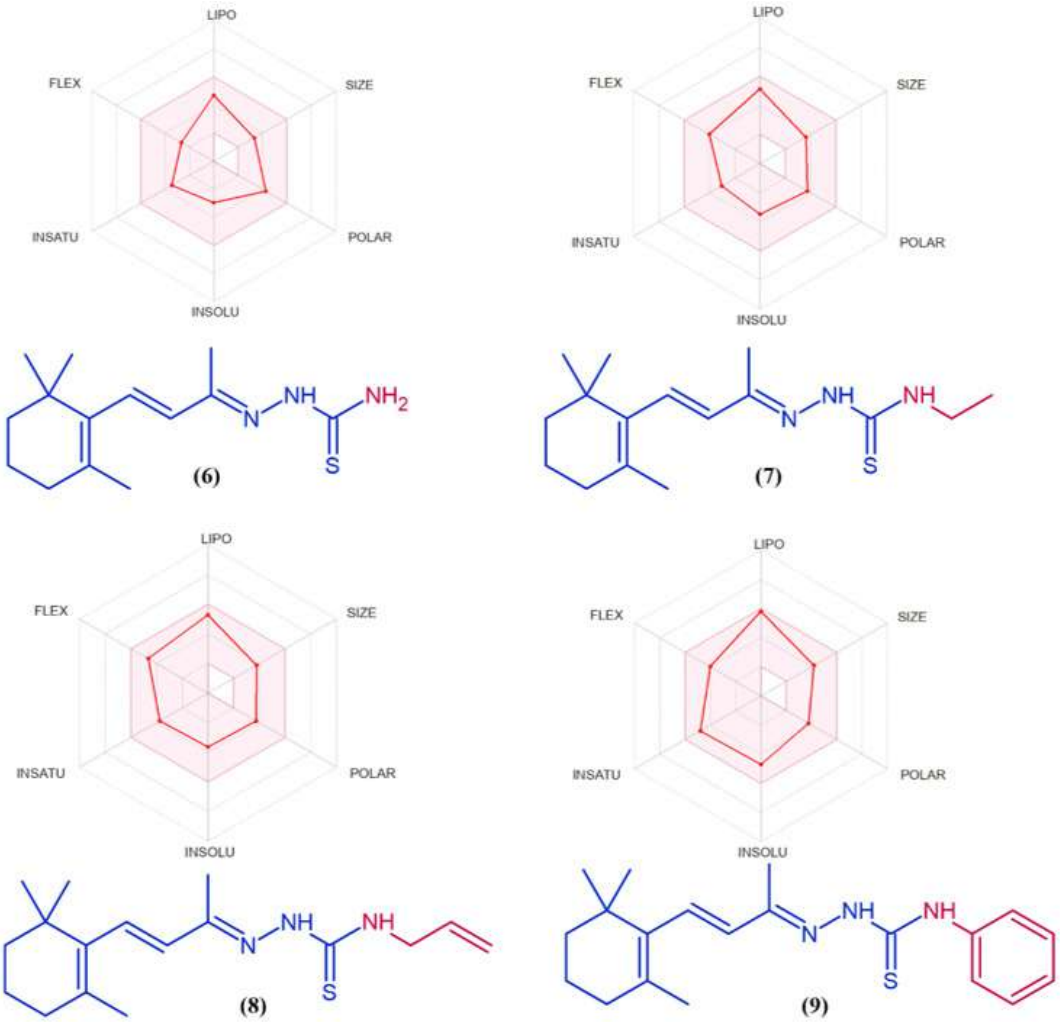


Figure 8. Diagrams of some essential ADME parameters of thiosemicarbazones 6-9.

Table 1. ADME parameters calculated for thiosemicarbazones 6-9

Compusul	logP	M, g/mol	TPSA, Å²	Rotatable bonds
6	3.12	265.42	82.5	4
7	3.82	293.47	68.51	6
8	4.06	305.48	68.51	7
9	4.72	341.51	68.51	6

logP – octanol-water partition coefficient, M – molar mass, TPSA- topological polar surface area

The SIZE parameter evaluates the molar mass of the compound. The optimal range for biologically active compounds is considered to be between 150-500 g/mol. None of the synthesized compounds violate this rule. In turn, the POLAR parameter evaluates the polarity of the compound or the topological polar surface area.

This parameter is very important because it largely determines whether the compound will cross the blood-brain barrier or not. If the compound crosses this barrier, it means that it can interact with the human central nervous system and, respectively, can cause undesirable adverse effects related to this. Figure 9 shows a diagram in which substances are distributed according to their logP and TPSA values and are marked as either passing through the blood-brain barrier or not.

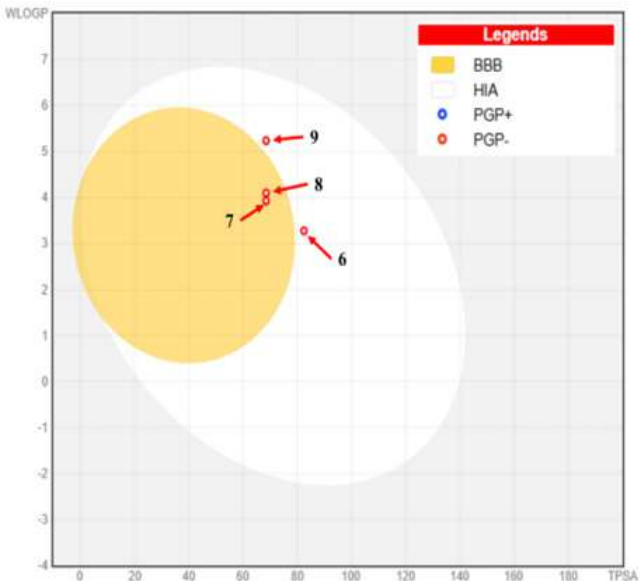


Figure 9. “Boiled-egg” diagram (logP/TPSA) for the synthesised thiosemicarbazones 6-9.

Only compounds **6** and **9** do not cross the blood-brain barrier, which means that they have the potential to have fewer adverse effects. Another important factor derived from Figure 9 is that the synthesized compounds will have high gastrointestinal adsorption. The FLEX parameter indicates the flexibility of the molecule - the number of rotatable bonds. It is considered that the optimal number for a biologically active molecule should be less than 10.

In addition, it was established that all compounds comply with the most popular and frequently used “drug likeness rules” or rules regarding similarity to drugs. These data are shown in Table 2. The basic rule is the rule of Lipinski, and the rest show some modifications introduced by researchers in the pharmaceutical field. It is generally recognized that substances that do not violate these rules have a much better potential to become drugs.

Table 2. Compliance with most frequently used drug likeness rules

Compound	Rule				
	Lipinski	Ghose	Veber	Egan	Muegge
6	+	+	+	+	+
7	+	+	+	+	+
8	+	+	+	+	+
9	+	+	+	+	+

Antioxidant assay

The antioxidant activity of the synthesized compounds was investigated using the DPPH method. Data from the Table 3 indicates that some of the tested compounds exhibit antioxidant activity almost twice as good as the reference compound ascorbic acid. The best result is shown by the compound **8**, with an IC_{50} at a concentration of 17.5 μM and compound **6** haven’t shown a significant activity in comparison with reference compound.

Table 3. DPPH IC_{50} concentrations of tested compounds.

Compound	IC_{50}, μM	SD
6	>32.6	±0.92
7	18.2	±0.51
8	17.5	±0.45
9	17.6	±0.54
Ascorbic acid	32.6	±0.90

CONCLUSIONS

In total four thiosemicarbazones based on β-ionone and their derivatives were synthesized. Their structure was confirmed by NMR spectroscopy. ADME analysis revealed the positive pharmacological profile of the synthesized compounds. Moreover, the synthesized compounds exhibit DPPH radical inhibition activity almost twice as good as ascorbic acid used as a reference compound, indicating an increased potential for antioxidant activity.

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