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Antioxidant properties of some 4-arylimino-thiazolidin-2-ones

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A B S T R A C T

In the present work, we report an efficient synthesis and antioxidant activity evaluation of some 4-arylimino-thiazolidin-2-ones. The structures of target substances were confirmed through ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The antioxidant activity of the synthesized compounds was measured *in vitro* by the method of scavenging effect on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. Notably, antioxidant activity was identified for the first time among 4-arylimino-thiazolidin-2-ones.

1. Introduction

In recent decades, the theory of free radical genesis of various pathological conditions in the human body has been significantly supported by new, substantial data, emphasizing its correctness and relevance.[1] This is confirmed by the emergence of the concept of "free radical pathology," which underlies the development of premature aging of the body and about 60% of the most common diseases.[2] Normally, the regulation of the production of activated oxygen metabolites and free radicals in human tissues and organs is carried out by the antioxidant system, which includes compounds of different chemical natures. Despite its high efficiency, this system is not always capable of protecting the human body from the development of oxidative stress.[3] According to modern concepts, a decrease in the ratio of prooxidants/antioxidants is considered as the most significant factor opposing the initiation of the process of free radical oxidation and the occurrence of oxygen toxicity.[4] There is no doubt about the medical significance of synthetic antioxidants as preventive therapy.[5]

The pharmaceutical market of modern antioxidants is represented by both natural compounds and synthetic drugs, characterized by many side effects and contraindications or instability during long-term storage. Most of the obtained compounds do not reach clinical application due to their high toxicity, poor solubility in water, nonspecific action and a number of other side effects.[6] Therefore, the issue of developing new, more active antioxidants remains relevant.

Nitrogen-based heterocycles are an extremely important class of organic substances widely used in medicinal chemistry, since more than 60% of drugs and more than 85% of biologically active substances reported in the literature contain a Nitrogen-containing heterocycle in their structure.[7] The study of the reactivity of thiazole or thiazolidone derivatives and the implementation of their chemical transformations is a promising direction in the search for new biologically active substances among nitrogen-containing heterocycles.[8,9] This is due to the wide spectrum of biological activity within this

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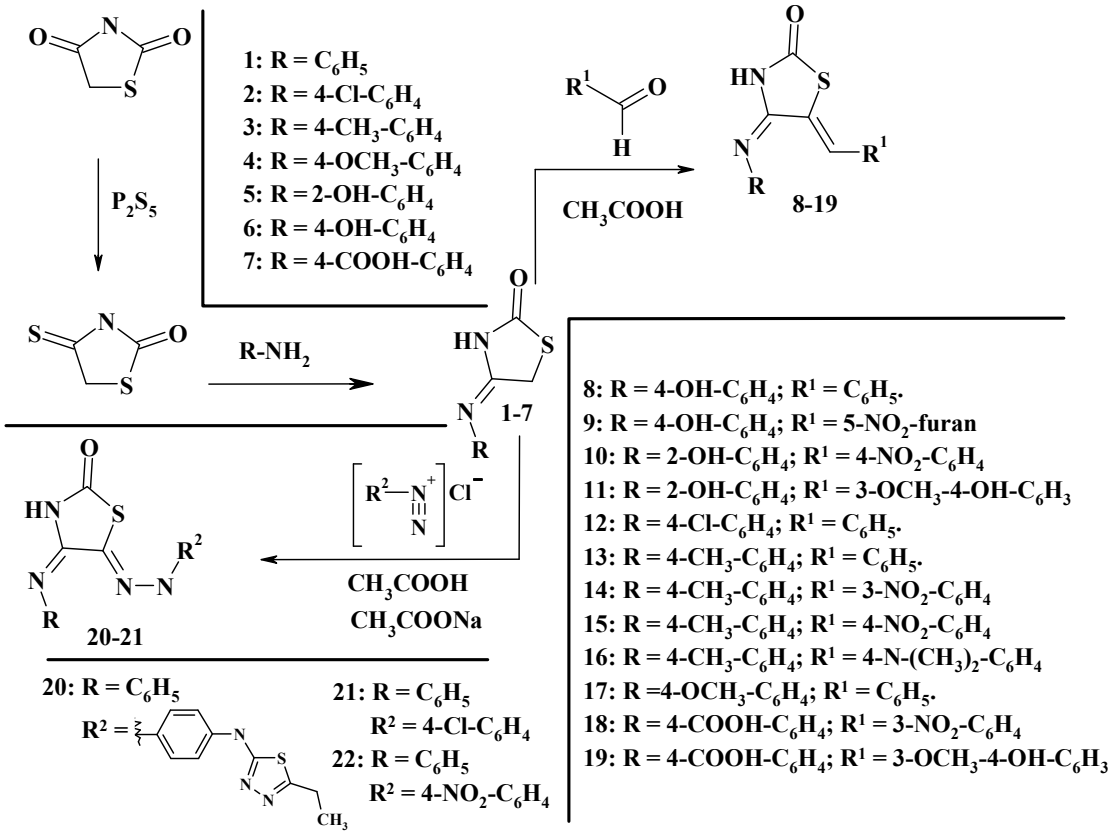
class of compounds, as well as the presence of multiple reactive centers, which allows for versatile modification of the original structure.[10-18] 4-Iminothiazolidones are ones of the most hardly accessible and insufficiently studied analogs among this class of organic compounds. It should be noted that the 4-iminothiazolidinones we are considering are characterized by the presence of three tautomeric forms, characterized by different stability.[19,20] The recent data published in the scientific literature highlighted a diversity of biological effects exhibited by 4-iminothiazolidinones. They have been reported to have high anti-inflammatory,[21] antitumor,[22,23] antioxidant[24,25] and fungicidal[26] activities. It is worth noting that the use of 4-iminothiazolidones with an unsubstituted vicinal carbon atom provides access to various types of condensed heterocyclic systems.[27-33] Also this class of compounds has also been used as sensitive analytical reagents.[34,35] Given the facts mentioned above, the development of 4-iminothiazolidinone derivatives synthesis methods and the evaluation of their antioxidant activity remain research priorities.

2. Results and Discussion

2.1 Chemistry

As a continuation of our research work in reference to the design of biologically active azaheterocycles,[36-40] in this article we reported to synthesize a series of 4-iminothiazolidinones by means of the core heterocycle structural modification with further pharmacological screening on antioxidant activity. Synthetic approach to the target compounds was based on structure modification of azolidinone ring formed in [2+3]-cyclocondensation reaction and modifying it in the positions 4 and 5. Based on the arguments mentioned above the first step was the synthesis of previously described 4-thioxo-thiazolidin-2-one (isorhodanine).[41] This compound was obtained by the thionation reaction basic scaffold with phosphorus pentasulphide. Obtained at this stage 4-thioxo-thiazolidin-2-one was introduced into the aminolysis reaction according to a known method.[19] As a result of this transformation, it was possible to obtain the corresponding 4-arylimino-thiazolidin-2-ones **1-7 (Scheme)**.[19] Considering the variety of thiazolidinones, the 5-ylidene subtype is of a special interest as source of lead-compounds and drug-candidates, following the thesis about decisive role of the presence and nature of C^5 substituent in the thiazolidinone core for realization of the biological effects.[9] The synthesized methylene active derivatives **1-7** was readily reacted with aromatic aldehydes to produce 5-arylidene derivatives **8-19**, using a Knoevenagel condensation procedure (medium - acetic acid, catalyst - monoaminoethanol) (**Scheme**). The presence of an active methylene group in C^5 position also provides an entry for its utilization in the azo coupling reaction with aryldiazonium salts. It was found that compound **1** reacts with aryldiazonium salts, leading to appropriate 5-aryl-hydrazono-4-phenylimino-thiazolidin-2-ones **20-22 (Scheme 1)**.



Scheme 1. Synthesis of some 4-arylimino-thiazolidin-2-ones

Obtained compound structures were confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures.

2.2 Antioxidant activity

The antioxidant activity was determined free radical on the basis of free radical scavenging activity of 2,2-diphenyl-1-picrylhydrazyl (DPPH). The DPPH method is described as a simple, rapid and convenient method for screening of many samples for radical scavenging activity. DPPH radical has found many applications due to its high stability in a methanolic solution and intense purple color. In its oxidized form, the DPPH radical has an absorbance maximum at a wavelength of 517 nm. The absorbance decreases when antioxidants reduce the radical. Its reduction affords 2,2-diphenyl-1-picrylhydrazine (DPPH-H), or the corresponding anion ($DPPH^-$) in basic medium. The DPPH radical acts as a scavenger for other odd-electron species which afford para-substitution products at phenyl rings.[42-43] These advantages make the DPPH method interesting for testing newly synthesized compounds to scavenge radicals and to find out antioxidant drug candidates.

In the present paper, we demonstrate a modified spectrophotometric method making use of the DPPH radical and its specific absorbance properties. The free-radical-scavenging activity of each compound was assayed using a stable DPPH and was quantified by decolorization the solution being mixed with DHHP at a wavelength of 517 nm. The absorbance of DPPH solution in ethanol (150 mmoles/l) was measured as 0.77. The absorbances and free-radical-scavenging activities % inhibitions of standard (ascorbic acid) and each compound are listed in a **Table 1** below.

Table 1. Values of Absorbance and % Inhibition of 4-arylimino-thiazolidin-2-ones

The Compound or Standard	Absorbance of a Sample, A_s	% Inhibition
Ascorbic acid	0.580±0.015	24.7
8	0.592±0.015	23.1
9	0.644±0.020	16.4
10	0.621±0.020	19.4
11	0.560±0.015	27.3
12	0.710±0.030	7.8
13	0.705±0.025	8.5
14	0.733±0.035	4.8
15	0.673±0.025	12.5
16	0.668±0.025	13.3
17	0.696±0.025	9.6
18	0.543±0.010	29.4
19	0.615±0.020	20.1
20	0.731±0.035	5.1
21	0.720±0.030	6.4
22	0.740±0.035	3.9

The antioxidant activity evaluation results showed that, in general, most of the tested compounds possess insignificant free radical scavenging effect being in the range of 3.9-16.4%. The compounds **8**, **10** and **19** possessed the antioxidant activity in the range of 19.4–23.1% which is comparable to the effect of Ascorbic acid. However, when compared with existing antioxidants, some of our compounds were found to be more potent. The antioxidant evaluation test for compounds **11** and **18** gave the result at the level of 27.3. and 29.4 % inhibition indicating these compounds were more potent than comparison drug.

3. Conclusions

A series of 4-arylimino-thiazolidin-2-one derivatives possessing antioxidant activity were prepared by the structural modification of the core heterocycle in C^4 and C^5 positions. We have shown that the proposed approaches provide the possibility to design thiazolidin-2-ones diversity with a considerable chemical novelty. When compared with existing antioxidants, some of our compounds were found to be more potent. Further optimization of the structure to improve biological activity is currently in progress.

4. Experimental

4.1 Chemistry

All chemicals were of analytical grade and commercially available. When performing the synthetic part of the work, the reagents of the company Merck (Germany) and Sigma-Aldrich (USA) were used. All reagents and solvents were used without further purification and drying. All the melting points were determined in an open capillary and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Mercury 400 (Agilent Technologies, San Francisco, USA), instrument with TMS or deuterated solvent as an internal reference, while ^{13}C NMR spectra of all compounds were recorded on a Bruker Avance DRX-500 spectrometer (125 MHz). Mass spectra were run using Agilent 1100 series LC/MSD (Agilent Technologies, San Francisco, USA) with an API–ES/APCI ionization mode. Elemental analysis was performed on an Elementar Vario L cube instrument (Elementar Analysen systeme GmbH, Hanau, Germany), yielding satisfactory results for new compounds (C±0.17, H±0.21, N±0.19).

General procedure for the preparation of 5-arylidene-4-arylimino-thiazolidin-2-ones ***8-19***. 0.005 mol of the corresponding 4-arylimino-thiazolidin-2-one, 0.005 mol of the corresponding aromatic aldehyde and a few drops of monoaminoethanol are added to 15 ml of acetic acid. The mixture is heated to boiling for 30 minutes. After cooling, the resulted crystalline precipitate is filtered, washed with water and dried. The obtained compounds are recrystallized from acetic acid.

5-Benzylidene-4-(4-hydroxy-phenylimino)-thiazolidin-2-one ***8***.

Yield: 65%; mp 242 ºC; ^{1}H NMR, δ, ppm: 10.67 (s, 1H, NH), 9.69 (s, 1H, OH), 8.17 (s, 1H, CH), 7.63 (d, 2H, *J* = 7.8 Hz, C_6H_4-OH), 7.57 (t, 2H, *J* = 7.4, 7.9 Hz, C_6H_5), 7.48 (d, 1H, *J* = 7.5 Hz, C_6H_5), 7.38 (s, 1H, C_6H_5), 7.22 (d, 2H, *J* = 7.8 Hz, C_6H_4-OH), 6.65 (d, 1H, *J* = 8.9 Hz, C_6H_5). ESI-MS: m/z 297 [M+H]+; anal. calcd. $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45. Found: C, 64.76; H, 4.11; N, 9.41.

4-(4-Hydroxy-phenylimino)-5-(5-nitro-furan-2-ylmethylene)-thiazolidin-2-one ***9***.

Yield: 72%; mp 218 ºC; ^{1}H NMR, δ, ppm: 10.75 (s, 1H, NH), 9.56 (s, 1H, OH), 8.07 (s, 1H, CH), 7.81 (d, 1H, *J* = 3.8 Hz, furan), 7.61 (d, 2H, *J* = 8.6 Hz, C_6H_4-OH), 7.16 (d, 1H, *J* = 4.0 Hz, furan), 6.83 (d, 2H, *J* = 8.6 Hz, C_6H_4-OH). ^{13}C NMR, δ, ppm: 176.43, 168.70, 155.55, 152.27, 151.97, 134.59, 129.48, 123.89, 117.44, 115.26, 112.74. ESI-MS: m/z 332 [M+H]+; anal. calcd. $C_{14}H_9N_3O_5S$: C, 50.76; H, 2.74; N, 12.68. Found: C, 50.61; H, 2.77; N, 12.55.

4-(2-Hydroxy-phenylimino)-5-(4-nitro-benzylidene)-thiazolidin-2-one ***10***.

Yield: 70%; mp 265 ºC; ^{1}H NMR, δ, ppm: 10.59 (s, 1H, NH), 9.88 (s, 1H, OH), 8.37 (d, 2H, *J* = 8.8 Hz, C_6H_4-NO_2), 8.21 (s, 1H, CH), 7.84 (d, 2H, *J* = 8.7 Hz, C_6H_4-NO_2),7.43 (d, 1H, *J* = 7.9 Hz, C_6H_4-OH), 7.19 (t, 1H, *J* = 7.6 Hz, 7.9 Hz, C_6H_4-OH), 6.98 (d, 1H, *J* = 8.0 Hz, C_6H_4-OH), 6.89 (t, 1H, *J* = 7.5 Hz, 7.6 Hz, C_6H_4-OH). ^{13}C NMR, δ, ppm: 176.40, 172.35, 151.39, 147.16, 140.57, 133.51, 130.51, 128.37, 127.15, 125.81, 124.92, 124.32, 118.98, 116.29. ESI-MS: m/z 343 [M+H]+; anal. calcd. $C_{16}H_{11}N_3O_4S$: C, 56.30; H, 3.25; N, 12.31. Found: C, 56.22; H, 3.34; N, 12.26.

5-(4-Hydroxy-3-methoxy-benzylidene)-4-(2-hydroxy-phenylimino)-thiazolidin-2-one ***11***.

Yield: 73%; mp 230 ºC; ^{1}H NMR, δ, ppm: 10.37 (s, 1H, NH), 9.82 (s, 1H, OH), 9.79 (s, 1H, OH),8.05 (s, 1H, CH), 7.40 (d, 1H, *J* = 7.8 Hz, C_6H_4-OH), 7.15-7.18 (m, 1H, C_6H_4-OH), 7.09-7.13 (m, 2H, C_6H_3), 6.96 (d, 2H, *J* = 8.1 Hz, C_6H_3 + C_6H_4-OH), 6.84-6.88 (m, 1H, C_6H_4-OH), 3.85 (s, 3H, O-CH_3). ^{13}C NMR, δ, ppm: 177.63, 172.42, 151.28, 149.06, 147.95, 129.36, 127.91, 127.11, 125.46, 125.34, 124.61, 124.32, 118.93, 116.20, 113.12, 55.54. ESI-MS: m/z 344 [M+H]+; anal. calcd. $C_{17}H_{14}N_2O_4S$: C, 59.64; H, 4.12; N, 8.18. Found: C, 59.58; H, 4.03; N, 8.12.

5-Benzylidene-4-(4-chloro-phenylimino)-thiazolidin-2-one ***12***.

Yield: 65%; mp 212 ºC; ^{1}H NMR, δ, ppm: 10.79 (s, 1H, NH), 8.17 (s, 1H, CH), 7.81 (d, 2H, *J* = 7.7 Hz, C_6H_4-Cl), 7.64 (d, 2H, *J* = 7.5 Hz, C_6H_4-Cl), 7.57 (t, 2H, *J* = 7.3 Hz, *J* = 7.8 Hz, C_6H_5), 7.44-7.50 (m, 2H, C_6H_5), 7.57 (t, 1H, *J* = 7.4 Hz, C_6H_5). ESI-MS: m/z 316 [M+H]+; anal. calcd. $C_{16}H_{11}ClN_2OS$: C, 61.05; H, 3.52; N, 8.90. Found: C, 60.97; H, 3.44; N, 8.96.

5-Benzylidene-4-p-tolylimino-thiazolidin-2-one ***13***.

Yield: 82%; mp 255 ºC; ^{1}H NMR, δ, ppm: 10.77 (s, 1H, NH), 8.15 (s, 1H, CH), 7.68 (d, 2H, *J* = 8.4 Hz, $\underline{C_6H_4}$-CH_3), 7.63 (dd, 2H, *J* = 7.9 Hz, C_6H_5), 7.57 (t, 2H, *J* = 7.3 Hz, *J* = 7.9 Hz, C_6H_5), 7.46-7.50 (m, 1H, C_6H_5), 7.27 (d, 2H, *J* = 8.1 Hz, $\underline{C_6H_4}$-CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR, δ, ppm: 177.80, 170.28, 135.90, 134.90, 134.22, 129.97, 129.68, 129.55, 129.27, 129.19, 128.53, 122.44, 20.54. ESI-MS: m/z 296 [M+H]+; anal. calcd. $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.44; H, 4.82; N, 9.49.

5-(3-Nitro-benzylidene)-4-p-tolylimino-thiazolidin-2-one ***14***.

Yield: 70%; mp 263-264 ºC; ^{1}H NMR, δ, ppm: 10.91 (s, 1H, NH), 8.39 (s, 1H, C_6H_4), 8.27 (dd, 1H, *J* = 8.2 Hz, C_6H_4), 8.20 (s, 1H, CH), 8.02 (d, 1H, *J* = 7.9 Hz, C_6H_4), 7.84 (t, 1H, *J* = 8.0 Hz, *J* = 7.9 Hz, C_6H_4), 7.64 (d, 2H, *J* = 8.4 Hz, $\underline{C_6H_4}$-CH_3), 7.25 (d, 2H, *J* = 8.4 Hz, $\underline{C_6H_4}$-CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR, δ, ppm: 176.05, 169.26, 148.19, 136.48, 136.01, 135.15, 133.88, 130.72, 129.29, 129.03, 123.40, 122.64, 120.22, 20.55. ESI-MS: m/z 341 [M+H]+; anal. calcd. $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38. Found: C, 60.14; H, 3.79; N, 12.43.

5-(4-Nitro-benzylidene)-4-p-tolylimino-thiazolidin-2-one ***15***.

Yield: 80%; mp 253 ºC; ^{1}H NMR, δ, ppm: 10.90 (s, 1H, NH), 8.37 (d, 2H, *J* = 8.8 Hz, C_6H_4), 8.19 (s, 1H, CH), 7.83 (d, 2H, *J* = 8.7 Hz, C_6H_4), 7.66 (d, 2H, *J* = 8.4 Hz, $\underline{C_6H_4}$-CH_3), 7.26 (d, 2H, *J* = 8.3 Hz, $\underline{C_6H_4}$-CH_3), 2.33 (s, 3H, CH_3). ESI-MS: m/z 341 [M+H]+; anal. calcd. $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38. Found: C, 60.22; H, 3.88; N, 12.41.

5-(4-Dimethylamino-benzylidene)-4-p-tolylimino-thiazolidin-2-one ***16***.

Yield: 49 %; mp 261-262 ºC; ^{1}H NMR, δ, ppm: 10.44 (s, 1H, NH), 8.02 (s, 1H, CH), 7.67 (d, 2H, *J* = 8.3 Hz, $\underline{C_6H_4}$-CH_3), 7.48 (d, 2H, *J* = 8.9 Hz, C_6H_4), 7.23 (d, 2H, *J* = 8.4 Hz, $\underline{C_6H_4}$-CH_3), 6.86 (d, 2H, *J* = 8.9 Hz, C_6H_4), 3.02 (s, 6H, N-

$(CH_3)_2$), 2.31 (s, 3H, CH_3). ^{13}C NMR, δ, ppm: 178.44, 170.26, 151.23, 136.07, 134.30, 132.83, 132.06, 131.87, 129.92, 129.09, 122.06, 121.66, 120.87, 112.10, 20.52. ESI-MS: m/z 339 [M+H]+; anal. calcd. $C_{19}H_{19}N_3O_3S$: C, 67.63; H, 5.68; N, 12.45. Found: C, 67.75; H, 5.59; N, 12.37.

*5-Benzylidene-4-(4-methoxy-phenylimino)-thiazolidin-2-one **17**.*

Yield: 62 %; mp 227 ºC; ^{1}H NMR, δ, ppm: 10.72 (s, 1H, NH), 8.11 (s, 1H, CH), 7.71 (d, 2H, *J* = 9.0 Hz, C_6H_4-O-CH_3), 7.62 (d, 2H, *J* = 7.7 Hz, C_6H_5), 7.56 (t, 2H, *J* = 7.4 Hz, *J* = 7.9 Hz, C_6H_5), 7.48 (t, 1H, *J* = 7.3 Hz, *J* = 7.2 Hz, C_6H_5), 7.02 (d, 2H, *J* = 9.0 Hz, C_6H_4-O-CH_3), 3.79 (s, 3H, O-CH_3). ^{13}C NMR, δ, ppm: 177.70, 170.20, 156.98, 134.25, 131.23, 129.91, 129.66, 129.46, 129.24, 128.31, 124.04, 113.92, 55.30. ESI-MS: m/z 313 [M+H]+; anal. calcd. $C_{17}H_{15}N_2O_2S$: C, 65.57; H, 4.86; N, 9.00. Found: C, 65.49; H, 4.93; N, 8.94.

*4-[5-(3-Nitro-benzylidene)-2-oxo-thiazolidin-4-ylideneamino]-benzoic acid **18**.*

Yield: 55 %; mp 216 ºC; ^{1}H NMR, δ, ppm: 12.96 (s, 1H, COOH),11.02 (s, 1H, NH), 8.41 (s, 1H, CH), 8.31-8.33 (m, 2H, C_6H_4-COOH), 8.03-8.06 (m, 3H, C_6H_4-NO_2), 7.98 (d, 2H, *J* = 8.5 Hz, C_6H_4-COOH), 7.87 (t, 1H, *J* = 7.5 Hz, *J* = 7.9 Hz, C_6H_4-NO_2). ^{13}C NMR, δ, ppm: 176.79, 166.75, 148.22, 135.86, 135.25, 130.94, 130.44, 130.17, 127.07, 126.42, 124.07, 123.83, 121.87, 119.68. ESI-MS: m/z 371 [M+H]+; anal. calcd. $C_{17}H_{11}N_3O_5S$: C, 55.28; H, 3.00; N, 11.38. Found: C, 55.36; H, 2.95; N, 11.44.

*4-[5-(4-Hydroxy-3-methoxy-benzylidene)-2-oxo-thiazolidin-4-ylideneamino]-benzoic acid **19**.*

Yield: 64 %; mp 204 ºC; ^{1}H NMR, δ, ppm: 12.81 (s, 1H, COOH), 10.76 (s, 1H, NH), 9.95 (s, 1H, OH), 8.12 (s, 1H, CH), 8.02 (d, 2H, *J* = 8.8 Hz, C_6H_3), 7.97 (d, 2H, *J* = 8.7 Hz, C_6H_4-COOH), 7.16 (d, 2H, *J* = 8.0 Hz, C_6H_4-COOH), 6.98 (d, 1H, *J* = 8.0 Hz, C_6H_3). ^{13}C NMR, δ, ppm: 178.62, 170.40, 166.73, 149.50, 148.01, 142.22, 130.77, 130.16, 126.91, 125.22, 124.78, 124.66, 121.41, 116.27, 113.38, 55.57. ESI-MS: m/z 372 [M+H]+; anal. calcd. $C_{18}H_{14}N_2O_5S$: C, 58.37; H, 3.81; N, 7.56. Found: C, 55.29; H, 3.87; N, 7.60.

*General procedure for the preparation of 5-aryl-hydrazono-4-phenylimino-thiazolidin-2-ones **20-22**.* 0.01 mol of the corresponding amine is dissolved in 3 ml of concentrated hydrochloric acid, after which 5 ml of water is added. The solution obtained at this stage, with cooling at a temperature below 2°C, is diazotized by adding 0.72 g of sodium nitrite dissolved in 3 ml of water. The resulting diazonium salt is added over 30 minutes to a stirred and cooled solution of 0.01 mol of 4-phenylimino-thiazolidin-2-one **1** previously diluted in 80 ml of glacial acetate acid containing 4 g of anhydrous sodium acetate (pH = 4.5-5.0). The mixture is left for 12 hours, after which it is poured into 200 ml of water. The precipitate is filtered, washed on the filter with water and dried. The obtained compounds are recrystallized from acetic acid.

*4-Phenylimino-5-{[4-(5-ethyl-[1,3,4]thiadiazol-2-ylamino)-phenyl]-hydrazono}-thiazolidin-2-one **20**.*

Yield: 60 %; mp >260 ºC; ^{1}H NMR, δ, ppm: 13.89 (s, 1H, NH), 10.81 (s, 1H, NH), 10.71 (s, 1H, NH), 7.80 (d, 2H, *J* = 7.8 Hz, N-phenyl), 7.66-7.73 (m, 4H, C_6H_4), 7.46 (t, 2H, *J* = 7.7 Hz, N-phenyl), 7.27 (t, 1H, *J* = 7.4 Hz, N-phenyl), 2.79-2.85 (m, 2H, CH_2), 1.21 (t, 3H, *J* = 7.5 Hz, CH_3). ^{13}C NMR, δ, ppm: 174.24, 167.99, 167.16, 159.72, 146.67, 137.57, 134.30, 133.40, 128.69, 127.20, 125.86, 123.01, 114.25, 23.64, 12.25. ESI-MS: m/z 425 [M+H]+; anal. calcd. $C_{19}H_{17}N_7OS_2$: C, 53.88; H, 4.05; N, 23.15. Found: C, 53.78; H, 3.99; N, 23.28.

*4-Phenylimino 5-[(4-chloro-phenyl)-hydrazono]-thiazolidin-2-one **21**.*

Yield: 75 %; mp 243-244 ºC; ^{1}H NMR, δ, ppm: 10.83 (s, 1H, NH), 10.47 (s, 1H, NH),), 8.05 (d, 2H, *J* = 7.9 Hz, C_6H_4), 7.78 (d, 2H, *J* = 8.0 Hz, N-phenyl), 7.65 (d, 2H, *J* = 8.0 Hz, C_6H_4), 7.48 (t, 2H, *J* = 7.8 Hz, N-phenyl), 7.27 (t, 1H, *J* = 7.4 Hz, N-phenyl). ESI-MS: m/z 330 [M+H]+; anal. calcd. $C_{15}H_{11}ClN_4OS$: C, 54.46; H, 3.35; N, 16.94. Found: C, 54.55; H, 3.41; N, 16.88.

*4-Phenylimino-5-[(4-nitro-phenyl)-hydrazono]-thiazolidin-2-one **22**.*

Yield: 90 %; mp 252-254 ºC; ^{1}H NMR, δ, ppm: 10.90 (s, 1H, NH), 10.67 (s, 1H, NH),), 8.20 (d, 2H, *J* = 8.7 Hz, C_6H_4), 7.82 (d, 2H, *J* = 7.7 Hz, N-phenyl), 7.71 (d, 2H, *J* = 8.8 Hz, C_6H_4), 7.47 (t, 2H, *J* = 7.9 Hz, N-phenyl), 7.26 (t, 1H, *J* = 7.4 Hz, N-phenyl). ESI-MS: m/z 342 [M+H]+; anal. calcd. $C_{15}H_{11}N_5O_3S$: C, 52.78; H, 3.25; N, 20.52. Found: C, 52.84; H, 3.20; N, 20.44.

4.2 Antioxidant activity

The effect of the studied compounds on DPPH radicals was estimated according to the method of Blois[42,43] with minor modifications. The solution of DPPH in ethanol at concentration of 150 μmoles/L (4 mL) was mixed with the compound or control solution in ethanol its concentration been 250 μmoles/L (0.2 mL). The reaction mixture was vortex mixed thoroughly and incubated at room temperature in the dark for 60 min. Simultaneously, a control was prepared by mixing ascorbic acid solution in ethanol (0.2 mL) mixed with of DPPH solution in ethanol (4 mL) without sample fraction. Reduction in the absorbance of the mixture was measured at 517 nm using ethanol as blank. Ascorbic acid was used as a standard. Also the absorbance of DPPH solution was measured. Percentage of free-radical-scavenging activity was expressed as percent inhibition and it was calculated using the following formula:

$$\%\ \text{Inhibition} = \frac{\grave{A}_{DPPH} - A_c}{A_{DPPH}} \cdot 100\ \%\ ;$$

where A_{DPPH} is the absorbance of DPPH free radicals' solution, A_c is the absorbance of a sample.
Each experiment was performed in triplicate and average values were recorded. Results are expressed as the means ± S.D.

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