

# Synthesis of some new 4-iminothiazolidine-2-ones as possible antioxidants agents

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## Abstract

Novel N<sup>3</sup> substituted derivatives of 4-iminothiazolidine-2-one were synthesised under the reactions of [2+3]cyclocondensation, thionation and aminolysis. The functionalisation of 3-phenyl-4-imino-thiazolydine-2-one was carried out in its C<sup>5</sup> position under condensation Knoevenagel and nitrosation reactions. The antioxidant activity of the synthesised compounds was evaluated *in vitro* by the method of their scavenging effect on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. When compared with existing antioxidants, some of our compounds were found to be more potent.

## Keywords

antioxidant activity, 4-iminothiazolidine-2-ones, synthesis

## Introduction

There is an increasing evidence of the implication of free radicals in a variety of diseases. Free radicals are being formed during normal cellular metabolism and they are known to contribute to healthy functions of the human body and development when they are not excessive. At high concentrations, free radicals can cause damage to cell structures, nucleic acids, lipids and proteins (Valko et al. 2006), leading to age-related degenerative diseases, cancer and a wide range of different human diseases (Amarowicz et al. 2010). The major aim of antioxidants in human diseases is to prevent damage caused by the action of reactive oxygen species. The development of new potent antioxidant agents is a major goal for pharmaceutical and

medicinal chemistry as it searches for the way of removing the excess of free radicals and, thus, it ameliorates their hazardous effects on human beings.

Thiazolidine derivatives are a known group of biologically active compounds in modern medical chemistry (Singh et al. 1981; Abhinit et al. 2009; Jain et al. 2012; Chhabria et al. 2016; Chaban et al. 2017a, 2018a), which are characterised by a wide and diverse spectrum of biological activity. Substances of the mentioned class have been successfully tested as having antiviral (Harnden et al. 1978), anti-inflammatory (Song et al. 1989; Nasr and Said 2003; Chaban et al. 2016, 2017b, 2019;), anti-tumour (Zhou et al. 2008; Chaban et al. 2012a), anti-diabetic (Norisada et al. 2017), antioxidant (Klenina et al. 2013, 2017; Chaban et al. 2013, 2018b), anti-microbial (Vicini et al. 2018), tu-

berculostatic (Chaban et al. 2014) and other types of pharmacological activity. 4-Iminothiazolidine-2-one derivatives have also been used as sensitive analytical reagents (Lozynska et al. 2015; Tymoshuk et al. 2019) and the basic scaffold for the synthesis of condensed derivatives based on 4-azolidones (Chaban et al. 2012b).

4-Iminothiazolidine-2-ones, in comparison with isomeric 2-imino derivatives, have been insufficiently studied in modern organic and pharmaceutical chemistry. Taking into account these circumstances, the synthesis of new substances, as potential drug-like molecules, is relevant.

The objective of the present work was to synthesise a series of novel 4-iminothiazolidine-2-ones by the structural modification of the core heterocycle in its N<sup>3</sup> and C<sup>5</sup> positions for further pharmacological screening *in vitro* as antioxidants.

## Experimental part

### Materials and methods

All chemicals were of analytical grade and commercially available obtained from Sigma-Aldrich, Germany. All reagents and solvents were used without further purification and drying. <sup>1</sup>H NMR spectra of compounds in DMSO-d<sub>6</sub> solution were registered on a spectrometer Varian Mercury VX-400, USA (400 MHz), internal reference TMS. The elemental analysis experimental data on contents of Carbon, Hydrogen and Nitrogen correspond to those calculated (±0.3%) and were registered on a Elementar Vario L cube, Germany. Chemical shifts are reported in ppm units with use of δ scale.

Ascorbic acid was purchased from a medical store.

### Chemistry

*General procedure for the synthesis 3-aryl-4-imino-thiazolidine-2-ones (1a-d).* The mixture of the 25% ammonia solution (5 mmol) and the appropriate 3-aryl-4-thioxo-thiazolidine-2-one (5 mmol) was refluxed for 15 min. On cooling, the crystalline precipitate was filtered off, washed with acetone and dried. The obtained compounds were re-crystallised from acetic acid.

*4-Imino-3-phenyl-thiazolidin-2-one (1a).* Yield 58%, m.p.= 245 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 5.83 (s, 2H, CH<sub>2</sub>), 6.90 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.22 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.39 (d, 2H, J = 7.7 Hz, C<sub>6</sub>H<sub>5</sub>), 8.50 (s, 1H, NH). Calcd for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>S: C, 56.23; H, 4.19; N, 14.57. Found %: C, 56.13; H, 4.07; N, 14.36.

*4-Imino-3-(4-nitro-phenyl)-thiazolidin-2-one (1b).* Yield 54%, m.p.= 230 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 5.81 (s, 2H, CH<sub>2</sub>), 7.25 (d, 2H, J = 8.1 Hz, C<sub>6</sub>H<sub>4</sub>), 7.48 (d, 2H, J = 7.3 Hz, C<sub>6</sub>H<sub>4</sub>), 8.53 (s, 1H, NH). Calcd for C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>3</sub>S: C, 45.57; H, 2.97; N, 17.71. Found %: C, 45.59; H, 2.88; N, 17.66.

*4-Imino-3-(4-chloro-phenyl)-thiazolidin-2-one (1c).* Yield 40%, m.p.= 197 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)

δ 5.64 (s, 2H, CH<sub>2</sub>), 7.12 (d, 2H, J = 7.9 Hz, C<sub>6</sub>H<sub>4</sub>), 7.38 (d, 2H, J = 8.1 Hz, C<sub>6</sub>H<sub>4</sub>), 8.51 (s, 1H, NH). Calcd for C<sub>9</sub>H<sub>7</sub>ClN<sub>2</sub>O<sub>2</sub>S: C, 47.69; H, 3.11; N, 12.36. Found %: C, 47.78; H, 3.19; N, 12.47.

*4-Imino-3-(4-fluoro-phenyl)-thiazolidin-2-one (1d).* Yield 45%, m.p.= 224 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 5.75 (s, 2H, CH<sub>2</sub>), 7.21 (d, 2H, J = 7.7 Hz, C<sub>6</sub>H<sub>4</sub>), 7.46 (d, 2H, J = 8.4 Hz, C<sub>6</sub>H<sub>4</sub>), 8.48 (s, 1H, NH). Calcd for C<sub>9</sub>H<sub>7</sub>FN<sub>2</sub>O<sub>2</sub>S: C, 51.42; H, 3.36; N, 13.33. Found %: C, 52.07; H, 3.28; N, 13.15.

*General procedure of synthesis of 5-arylidene derivatives 3-phenyl-4-iminothiazolidine-2-one (2a-2i).* To 15 ml of acetate acid, 0.005 mol of compound **1a**, 0.005 mol of the corresponding aromatic aldehyde and a few drops of mono-aminoethanol were added. The mixture is boiled for 30 minutes. The crystalline precipitate, which was obtained after cooling, is filtered off, washed with water and dried. The resulting compounds are recrystallised from acetate acid.

*5-(4-Fluoro-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (2a).* Yield 70%, m.p.= 260–262 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 6.93 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.28 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.44 (d, 2H, J = 7.7 Hz, C<sub>6</sub>H<sub>5</sub>), 7.42 (d, 2H, J = 8.5 Hz, C<sub>6</sub>H<sub>4</sub>), 7.59–7.64 (m, 2H, C<sub>6</sub>H<sub>4</sub>), 7.84 (s, 1H, CH), 8.54 (s, 1H, NH). Calcd for C<sub>16</sub>H<sub>11</sub>FN<sub>2</sub>O<sub>2</sub>S: C, 64.42; H, 3.72; N, 9.39. Found %: C, 64.25; H, 3.74; N, 9.33.

*5-(4-Chloro-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (2b).* Yield 61%, m.p.= 253–254 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 6.89 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.22 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.36 (d, 2H, J = 7.7 Hz, C<sub>6</sub>H<sub>5</sub>), 7.45 (d, 2H, J = 8.5 Hz, C<sub>6</sub>H<sub>4</sub>), 7.54 (d, 2H, J = 8.5 Hz, C<sub>6</sub>H<sub>4</sub>), 7.83 (s, 1H, CH), 8.57 (s, 1H, NH). Calcd for C<sub>16</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub>S: C, 61.05; H, 3.52; N, 8.90. Found %: C, 61.27; H, 3.44; N, 8.85.

*5-(4-Methoxy-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (2c).* Yield 65%, m.p.= 248 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.79 (s, 1H, O-CH<sub>3</sub>), 6.91 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.15 (d, 2H, J = 8.8 Hz, C<sub>6</sub>H<sub>5</sub>), 7.31 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.47 (d, 2H, J = 8.7 Hz, C<sub>6</sub>H<sub>4</sub>), 7.55 (d, 2H, J = 8.8 Hz, C<sub>6</sub>H<sub>4</sub>), 7.79 (s, 1H, CH), 8.55 (s, 1H, NH). Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S: C, 65.79; H, 4.55; N, 9.03. Found %: C, 65.07; H, 4.59; N, 9.15.

*5-(3,4-Dimethoxy-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (2d).* Yield 55%, m.p.= 240–242 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.77 (s, 1H, O-CH<sub>3</sub>), 3.81 (s, 1H, O-CH<sub>3</sub>), 6.95 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.04 (s, 1H, J = 8.5 Hz, C<sub>6</sub>H<sub>5</sub>), 7.15 (d, 2H, J = 8.8 Hz, C<sub>6</sub>H<sub>5</sub>), 7.26 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.42 (d, 2H, J = 7.7 Hz, C<sub>6</sub>H<sub>3</sub>), 7.77 (s, 1H, CH), 8.51 (s, 1H, NH). Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S: C, 63.51; H, 4.74; N, 8.23. Found %: C, 63.11; H, 4.78; N, 8.16.

*5-(4-Hydroxy-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (2e).* Yield 52%, m.p.= 220 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 6.89 (d, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>4</sub>), 6.95 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.22 (t, 2H, J = 8.1 Hz, C<sub>6</sub>H<sub>5</sub>), 7.37 (d, 2H, J = 7.6 Hz, C<sub>6</sub>H<sub>5</sub>), 7.44 (d, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>4</sub>), 7.77 (s, 1H, CH), 8.54 (s, 1H, NH), 10.25 (s, 1H, OH). Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S: C, 64.95; H, 4.08; N, 9.45. Found %: C, 65.05; H, 4.14; N, 9.33.

5-(4-Hydroxy-3-methoxy-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (**2f**). Yield 57%, m.p.= 235–236 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.81 (s, 1H, O-CH<sub>3</sub>), 6.93 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.05 (s, 1H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.20 (d, 2H, J = 8.1 Hz, C<sub>6</sub>H<sub>5</sub>), 7.35 (t, 2H, J = 7.6 Hz, C<sub>6</sub>H<sub>5</sub>), 7.46 (d, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.79 (s, 1H, CH), 8.52 (s, 1H, NH), 9.91 (s, 1H, OH). Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S %: C, 62.56; H, 4.32; N, 8.58. Found %: C, 62.09; H, 4.33; N, 8.49.

5-(4-Methyl-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (**2g**). Yield 57%, m.p.= 212 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 2.12 (s, 1H, CH<sub>3</sub>), 6.88 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.11 (d, 2H, J = 8.8 Hz, C<sub>6</sub>H<sub>5</sub>), 7.29 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.38 (d, 2H, J = 7.9 Hz, C<sub>6</sub>H<sub>4</sub>), 7.55 (d, 2H, J = 7.9 Hz, C<sub>6</sub>H<sub>4</sub>), 7.87 (s, 1H, CH), 8.60 (s, 1H, NH). Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S %: C, 69.36; H, 4.79; N, 9.52. Found %: C, 69.25; H, 4.77; N, 9.49.

5-(4-Bromo-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (**2h**). Yield 68%, m.p.= 253 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 6.77 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.18 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.33 (d, 2H, J = 7.7 Hz, C<sub>6</sub>H<sub>5</sub>), 7.54 (d, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>4</sub>), 7.65 (d, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>4</sub>), 7.77 (s, 1H, CH), 8.51 (s, 1H, NH). Calcd for C<sub>16</sub>H<sub>11</sub>BrN<sub>2</sub>OS %: C, 53.49; H, 3.09; N, 7.80. Found %: C, 53.37; H, 3.12; N, 7.82.

5-(4-Nitro-benzylidene)-4-imino-3-phenyl-thiazolidin-2-one (**2i**). Yield 49%, m.p.= 269–270 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 6.87 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 6.96 (d, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>4</sub>), 7.24 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.41 (d, 2H, J = 7.7 Hz, C<sub>6</sub>H<sub>5</sub>), 7.52 (d, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>4</sub>), 7.77 (s, 1H, CH), 8.51 (s, 1H, NH). Calcd for C<sub>16</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S %: C, 59.07; H, 3.41; N, 12.92. Found %: C, 59.79; H, 3.44; N, 12.87.

4-Imino-3-phenyl-thiazolidine-2,5-dione 5-oxime (**3**). 0.05 mol of compound **1a** are added in 50 ml of 10% HCl, cooled to 0 °C and a solution of 10.5 g sodium nitrite in 25 ml of water is added to the suspension by dropping during stirring and cooling for 1 h. The mixture is left at room temperature for 12 hours. The precipitate is filtered off, washed with water, acetone and dried at 60 °C. Yield 65%, m.p.= 182 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 6.89 (t, 1H, J = 7.3 Hz, C<sub>6</sub>H<sub>5</sub>), 7.19 (t, 2H, J = 8.0 Hz, C<sub>6</sub>H<sub>5</sub>), 7.39 (d, 2H, J = 7.7 Hz, C<sub>6</sub>H<sub>5</sub>), 8.50 (s, 1H, NH), 10.05 (s, 1H, OH). Calcd for C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>S %: C, 48.86; H, 3.19; N, 18.99. Found %: C, 49.03; H, 3.21; N, 18.90.

## Free radical scavenging assays

The antioxidant activity was determined on the basis of the free radical scavenging activity of stable 2,2-Diphenyl-1-picrylhydrazyl (DPPH). The effect of the studied compounds on DPPH radicals was estimated according to the method of Blois (Blois 1958; Molyneux 2004) with minor modifications. The solution of DPPH in ethanol with a concentration of 150 μmoles/l (4 ml) was mixed with the compound or control solution in ethanol, its concentration being 250 μmoles/l (0.2 ml). The reaction mixture was thoroughly vortex-mixed and incubated at room temperature in the dark for 60 min. Simultaneously, a control was prepared as ascorbic acid solution in ethanol (0.2 ml) mixed with DPPH solution in ethanol (4 ml) without sample fraction. Reduction in the absorbance of the mixture

was measured at 540 nm using ethanol as blank. Ascorbic acid was used as a standard. The absorbance of DPPH solution was also measured. The percentage of free-radical-scavenging activity was expressed as percent inhibition and it was calculated using the following formula:

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

where A<sub>DPPH</sub> is the absorbance of DPPH free radicals solution, A<sub>c</sub> 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.

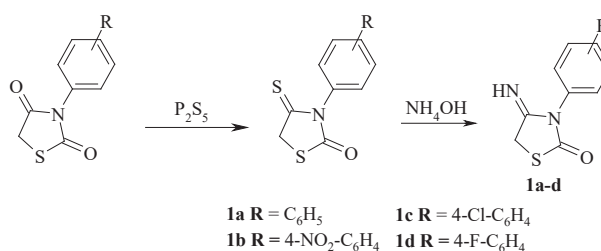
## Results and discussion

### Chemistry

A classical approach to the formation of the 4-thiazolidone ring is the reaction of [2+3]-cyclocondensation. The corresponding 3-aryl-thiazolidine-2,4-diones obtained by the known method (Komaritsa 1970) was introduced into the thionation reaction with phosphorus pentasulphide, which led to yielding the corresponding 3-aryl-4-thioxo-thiazolidine-2-ones. These substances are obtained under conditions of similar synthesis of the known 4-thioxo-thiazolidin-2-one. The synthetic potential of the resulting compounds allowed them to react with a 25% aqueous ammonia solution with the generation 3-aryl-4-imino-thiazolidine-2-ones (**1a-d**). The reaction mixture reflux for 15 min in 25% aqueous ammonia solution was the optimal condition for compounds **1a-d** formation proceeding in good yields (Scheme 1).

This transformation was made possible by the fact that 3-aryl-4-thioxo-thiazolidine-2-ones are cyclic thioamides and, as a consequence, have a significant activity of the thiol group resulting from the greater electrophilicity of the carbon atom in thiocarbonyl group of the mentioned compounds as compared to the carbonyl position of C<sup>4</sup> 4-aryl-thiazolidine-2,4-diones. One of the proofs of the obtained compounds structure is their acid hydrolysis to the known 3-aryl-thiazolidine-2,4-diones (Scheme 2):

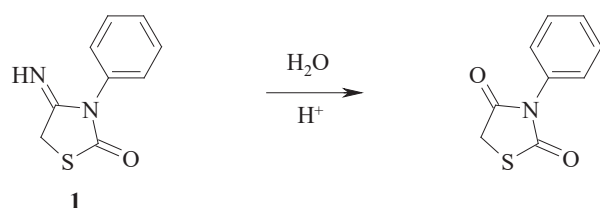
The methylene group presence in C<sup>5</sup> position of compound **1a** provides an entry for 5-arylidene derivatives 3-phenyl-4-iminothiazolidine-2-one (**2a-i**). Acetic acid



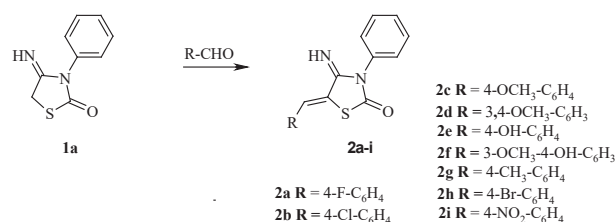
**Scheme 1.** Synthesis of 3-aryl-4-imino-thiazolidine-2-ones (**1a-d**).

was found to be the most suitable medium for the Knoevenagel condensation of compound **1a** with aromatic aldehydes. The synthetic strategy developed showed the high yielding compounds **2a-i** may be achieved by using monoaminoethanol as a catalyst (Scheme 3).

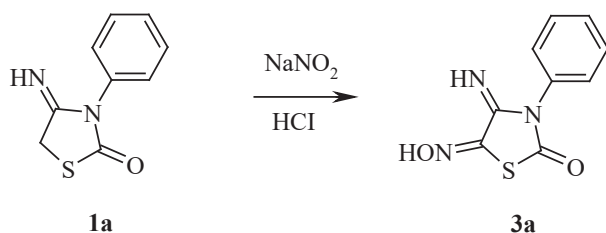
The next stage of our work was the further functionalisation of compound **1a** in position C<sup>5</sup>, in particular, the reaction of nitrosation of the mentioned heterocycle with nitric acid was investigated. It was found that compound **1a** reacts with nitric acid formed by the interaction of sodium nitrite with hydrochloric acid. As a result of the reaction, the corresponding 4-imino-3-phenyl-thiazolidine-2,5-dione 5-oxime (**3**) is formed (Scheme 4).



**Scheme 2.** Hydrolysis to the known 3-aryl-thiazolidine-2,4-diones.



**Scheme 3.** Synthesis of 5-arylidene derivatives 3-phenyl-4-iminothiazolidine-2-one (**2a-i**).



**Scheme 4.** Synthesis of 4-imino-3-phenyl-thiazolidine-2,5-dione 5-oxime (**3**) under the nitrosation reaction.

The structures of the obtained compounds were confirmed by <sup>1</sup>H NMR spectroscopy and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures. The <sup>1</sup>H NMR spectra of all compounds show the protons signals of the imino group in the thiazolidine ring as a singlet in the 8.48–8.57 ppm. The spectra of compounds **1a-d** show the signal of methylene group at the C<sup>5</sup> position as a singlet at 5.64–5.83 ppm. The spectrum of compound **1a** shows the signal of the phenyl radical as a duplet and triplet at 7.22 and 7.39 ppm. The lack of the methylene group signals for compounds **2a-i** proves the Knoevenagel condensation of the basic scaffold.

## Antioxidant activity in vitro evaluation

The antioxidant activity was determined on the basis of the free radical scavenging activity of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. The DPPH radical has found many applications due to its high stability in a methanolic solution and its having an intense purple colour. In its oxidised form, the DPPH radical has an absorbance maximum centred at a wavelength about 540 nm. The absorbance decreases when the radical is reduced by antioxidants. Its reduction affords 2,2-diphenyl-1-picrylhydrazine (DPPH-H) or the corresponding anion (DPPH<sup>-</sup>) in basic medium. The DPPH radical acts as a scavenger for other odd-electron species which provide(?) *para*-substitution products at phenyl rings.

The DPPH method is described as a simple, rapid and convenient method for screening of many samples for radical scavenging activity. These advantages make the DPPH method interesting for testing newly synthesised compounds to scavenge radicals and to identify promising antioxidant drug candidates.

In the present paper, we demonstrate that the modified spectrophotometric method uses the DPPH radical and its specific absorbance properties. The free-radical-scavenging activities of each compound were assayed using a stable DPPH and were quantified by decolourisation the solution being mixed with DHHP at a wavelength of 540 nm. The absorbance of DPPH solution in ethanol (150 μ moles/l) was measured as 0.770. The absorbances and free-radical-scavenging activities percentage inhibitions of standard (ascorbic acid) and each compound are listed in Table 1.

Antioxidant activity evaluation results showed that most of the researched compounds have a small effect on

**Table 1.** Values of absorbance and % inhibition of some novel 4-iminothiazolidine-2-ones.

The compound or standard	Absorbance of a sample, A <sub>s</sub>	% Inhibition	The compound or standard	Absorbance of a sample, A <sub>s</sub>	% Inhibition
Control	0.770±0.025	–	<b>2d</b>	0.731±0.020	5.05
<b>1a</b>	0.689±0.015	10.50	<b>2e</b>	0.738±0.025	4.11
<b>1b</b>	0.713±0.020	7.41	<b>2f</b>	0.707±0.025	8.17
<b>1c</b>	0.731±0.020	5.03	<b>2g</b>	0.720±0.020	6.52
<b>1d</b>	0.730±0.020	5.22	<b>2h</b>	0.679±0.020	11.83
<b>2a</b>	0.747±0.025	3.05	<b>2i</b>	0.572±0.015	25.65
<b>2b</b>	0.708±0.020	8.08	<b>3a</b>	0.561±0.015	27.15
<b>2c</b>	0.711±0.020	7.63	<b>Ascorbic acid</b>	0.580±0.015	24.68

the release of free radicals in the range 3.05% - 11.83%. c (25.65%, 27.15%) exceeding that for ascorbic acid. Thus, the structure of the substituents in the 5 position of 3-phenyl-4-iminothiazolidin-2-one showed that 4-bromo-benzylidene and 4-nitro-benzylidene increases the antioxidant activity compared with the basic scaffold.

## Conclusions

A series of novel 4-iminothiazolidine-2-ones derivatives, possessing antioxidant activity, were prepared by

the structural modification of the core heterocycle in N<sup>3</sup> and C<sup>5</sup> positions. We have shown that the proposed approaches and developed synthetic protocols provided the possibility to design 4-iminothiazolidine-2-ones diversity with a considerable chemical novelty involving [2+3] cyclocondensation, thionation, aminolysis, condensation Knoevenagel and nitrosation reactions. The pharmacological screening allowed identification of only two lead compounds whose free radical scavenging activity exceeded that for ascorbic acid. Further optimization of the structure to improve their activities is currently in progress.

## References

- Abhinit M, Ghodke M, Pratima N (2009) Exploring potential of 4-thiazolidinone: a brief review. *International Journal of Pharmacy and Pharmaceutical Sciences* 1: 47–64. <https://innovareacademics.in/journal/ijpps/Vol%201%20Issue%201/122.pdf>
- Amarowicz R, Estrella I, Hernandez T, Robredo S, Troszynska A, Kosinska A, Pegg R (2010) Free radical-scavenging capacity, antioxidant activity, and phenolic composition of green lentil (*Lens culinaris*). *Food Chemistry* 121: 705–711. <https://doi.org/10.1016/j.foodchem.2010.01.009>
- Blois MS (1958) Antioxidant determinations by the use of a stable free radical. *Nature* 181: 1199–1200. <https://doi.org/10.1038/1811199a0>
- Chaban TI, Panchuk RR, Klenina OV, Skorokhyd NR, Ogurtsov VV, Chaban IG (2012a) Synthesis and evaluation of antitumor activity of some thiazolo[4,5-*b*]pyridines. *Biopolymers and Cell* 28: 389–396. <https://doi.org/10.7124/bc.000075>
- Chaban TI, Zimenkovskii BS, Komaritsa JD, Chaban IG (2012b) Reaction of 4-iminothiazolidin-2-one with acetylacetone. *Russian Journal of Organic Chemistry* 48(2): 268–272. <https://doi.org/10.1134/S1070428012020170>
- Chaban TI, Ogurtsov VV, Chaban IG, Klenina OV, Komarytsia JD (2013) Synthesis and antioxidant activity evaluation of novel 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridines Phosphorus, Sulfur and Silicon and the Related Elements 188: 1611–1620. <https://doi.org/10.1080/10426507.2013.777723>
- Chaban T, Klenina O, Drapak I, Ogurtsov V, Chaban I, Novikov V (2014) Synthesis of some novel thiazolo[4,5-*b*]pyridines and their tuberculostatic activity evaluation. *Chemistry and Chemical Technology* 89: 287–292. <https://doi.org/10.23939/chcht08.03.287>
- Chaban TI, Klenina OV, Zimenkovsky BS, Chaban IG, Ogurtsov VV, Shelepeten LS (2016) Synthesis of novel thiazolo[4,5-*b*]pyridines as potential biologically active substances. *Der Pharma Chemica* 8(19): 534–542. <https://www.derpharmachemica.com/pharma-chemica/synthesis-of-novel-thiazolo-45b-pyridines-as-potential-biologically-active-substances.pdf>
- Chaban Z, Harkov S, Chaban T, Klenina O, Ogurtsov V, Chaban I (2017a) Recent advances in synthesis and biological activity evaluation of condensed thiazoloquinazolines: A review. *Pharmacia* 64(3): 52–66. <http://bsphs.org/?magasine=recent-advances-in-synthesis-and-biological-activity-evaluation-of-condensed-thiazoloquinazolines-a-review>
- Chaban T, Klenina O, Harkov S, Ogurtsov V, Chaban I, Nektegaev I (2017b) Synthesis of some new N<sup>3</sup> substituted 6-phenylazo-3*H*-thiazolo[4,5-*b*]pyridin-2-ones as possible anti-inflammatory agents. *Pharmacia* 64(4): 16–30. <http://bsphs.org/?magasine=synthesis-of-some-new-n3-substituted-6-phenylazo-3%20bd-thiazolo45-bpyridin-2-ones-as-possible-anti-inflammatory-agents>
- Chaban T, Klenina O, Chaban I, Ogurtsov V, Harkov S, Lelyukh M (2018a) Thiazolo[5,4-*d*]pyrimidines and thiazolo[4,5-*d*]pyrimidines: A review on synthesis and pharmacological importance of their derivatives. *Pharmacia* 65(2): 54–70. <http://bsphs.org/?magasine=thiazolo54-dpyrimidines-and-thiazolo45-dpyrimidines-a-review-on-synthesis-and-pharmacological-importance-of-their-derivatives>
- Chaban T, Matychuk V, Ogurtsov V, Chaban I, Harkov S, Nektegaev I (2018b) Synthesis and biological activity of some novel derivatives 5,7-dimethyl-6-phenylazo-3*H*-thiazolo[4,5-*b*]pyridine-2-one. *Pharmacia* 65 (4): 51–62. <http://bsphs.org/?magasine=synthesis-and-biological-activity-of-some-novel-derivatives-57-dimethyl-6-phenylazo-3%20bd-thiazolo45-bpyridine-2-one>
- Chaban TI, Ogurtsov VV, Matychuk VS, Chaban IG, Demchuk IL, Nektegayev IA (2019) Synthesis, anti-inflammatory and antioxidant activities of novel 3*H*-thiazolo[4,5-*b*]pyridines. *Acta Chimica Slovenica* 66: 103–111. <https://doi.org/10.17344/acsi.2018.4570>
- Chhabria MT, Patel S, Modi P, Brahmshatriya PS (2016) Thiazole: A review on chemistry, synthesis and therapeutic importance of its derivatives. *Current Topics in Medicinal Chemistry* 16: 2841–2862. <https://doi.org/10.2174/1568026616666160506130731>
- Harnden MR, Bailey S, Boyd MR, Taylor DR, Wright ND (1978) Thiazolinone analogues of indomycin with antiviral and antibacterial activity. *Journal of Medicinal Chemistry* 1: 82–87. <https://doi.org/10.1021/jm00199a700>
- Jain AK, Vaidya A, Ravichandran V, Kashaw SK, Agrawal RK (2012) Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorganic & Medicinal Chemistry* 20: 3378–3395. <https://doi.org/10.1016/j.bmc.2012.03.069>
- Klenina O, Drapak I, Chaban T, Ogurtsov V, Chaban I, Golos I (2013) QSAR studies of some thiazolo[4,5-*b*]pyridines as novel antioxidant agents: enhancement of activity by some molecular structure parameters. *Chemistry and Chemical Technology* 7: 397–404. <https://doi.org/10.23939/chcht07.04.397>
- Klenina O, Chaban T, Zimenkovsky B, Harkov S, Ogurtsov V, Chaban I, Myrko I (2017) Qsar modeling for antioxidant activity of novel N<sup>3</sup> substituted 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones. *Pharmacia* 64 (4): 49–71. <http://bsphs.org/?magasine=qsar-mod>

eling-for-antioxidant-activity-of-novel-n3-substituted-57-dimethyl-3%bd-thiazolo45-bpyridin-2-ones

Komaritsa ID (1970) Studies on azolidones and their derivatives. Preparation and properties of 4-iminothiazolid-2-one. *Chemistry of Heterocyclic Compounds* 4: 324–325. <https://doi.org/10.1007/BF00755270>

Lozynska L, Tymoshuk O, Chaban T (2015) Spectrophotometric studies of 4-[n'-(4-imino-2-oxo-thiazolidin-5-ylidene)-hydrazino]-benzenesulfonic acid as a reagent for the determination of Palladium. *Acta Chimica Slovenica* 62: 159–167. <https://doi.org/10.17344/acsi.2014.866>

Molyneux PJ (2004) The use of stable free radical diphenylpicrylhydrazyl (DPPH) for estimating antioxidant activity. *SciTechnol International Publisher of Science, Technology and Medicine* 26: 211–219. <http://www.thaiscience.info/Journals/Article/SONG/10462423.pdf>

Nasr MN, Said SA (2003) Novel 3,3a,4,5,6,7-hexahydroindazole and arylthiazolypyrazoline derivatives as anti-inflammatory agents. *Archiv der Pharmazie* 12: 551–559. <https://doi.org/10.1002/ardp.200300796>

Norisada N, Masuzaki H, Fujimoto M (2017) Antidiabetic and adipogenic properties in a newly synthesized thiazolidine derivative, FPF5-410. *Metabolism* 12: 1532–1537. <https://doi.org/10.1016/j.metabol.2004.06.020>

Singh SP, Parmar SS, Raman K, Stenberg VI (1981) Chemistry and biological activity of thiazolidinones. *Chemical Reviews* 81: 175–203. <https://doi.org/10.1021/cr00042a003>

Song Y, Connor DT, Doubleday R (1989) Synthesis, structure-activity relationships, and in vivo evaluations of substituted di-tert-butylphenols as a novel class of potent, selective, and orally active cyclooxygenase-2 inhibitors. Thiazolone and oxazolone series. *Journal of Medicinal Chemistry* 7: 1151–1160. <https://doi.org/10.1021/jm00121a021>

Tymoshuk O, Oleksiv L, Khvalbota L, Chaban T, Patsay I (2019) Spectrophotometric determination of ru(IV) using 5-hydroxyimino-4-imino-1,3-thiazolidin-2-one as a novel analytical reagent. *Acta Chimica Slovenica* 66: 62–69. <https://doi.org/10.17344/acsi.2018.4448>

Valko M, Rhodes C, Monocol J, Izakovic M, Mazur M (2006) Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chemico-Biological Interactions* 160: 1–40. <https://doi.org/10.1016/j.cbi.2005.12.009>

Vicini P, Geronikaki A, Incerti M (2018) 2-Heteroarylimino-5-benzylidene-4-thiazolidinones analogues of 2-thiazolylimino-5-benzylidene-4-thiazolidinones with antimicrobial activity: Synthesis and structure-activity relationship *Bioorganic and Medicinal Chemistry* 7: 3714–3724. <https://doi.org/10.1016/j.bmc.2008.02.001>

Zhou H, Wu S, Zhai S (2008) Design, synthesis, cytoselective toxicity, structure-activity relationships, and pharmacophore of thiazolidinone derivatives targeting drug-resistant lung cancer cells. *Journal of Medicinal Chemistry* 5: 1242–1251. <https://doi.org/10.1021/jm7012024>

## Appendix 1

