

Article

# Cardioprotective Activity of Some 2-Arylimino-1,3-Thiazole Derivatives

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**Abstract:** The article presents the synthesis of 2-arylimino-4-methyl-2,3-dihydro-1,3-thiazoles via Hantzsch reaction of thioureas and 3-chloropentane-2,4-dione or ethyl 2-chloro-3-oxobutanoate. The structure of synthesized compounds was confirmed by LCMS, <sup>1</sup>H, and <sup>13</sup>C NMR spectra. Cardioprotective activity of synthesized thiazole derivatives were studied in vitro on the isolated rings of the thoracic aorta of laboratory rats. Based on pharmacological studies, the tested compounds possessed a moderate to high cardioprotective effect. A prospective 1-[2-(4-methoxyphenylimino)-4-methyl-3-(4-methylpiperazine-1-yl)-2,3-dihydro-1,3-thiazole-5-yl] ethan-1-one hydrochloride **4c** was identified. The mentioned compound has delayed the development of constrictor responses of isolated rings of the thoracic rat aorta and exceeds the activity of L-carnitine by 18.2% and meldonium by 12.9%. The compound **4c** may be proposed as a potential cardioprotective agent for in-depth pharmacological studies.

**Keywords:** Hantzsch reaction; 1,3-thiazole derivatives; cardioprotective activity

## 1. Introduction

Nowadays, cardiovascular diseases are one of the main causes of mortality among the world population. Different approaches and the variety of compounds are discussed in the search for new cardioprotective agents and compounds aiming to decrease the cardiotoxicity of approved drugs [1–3]. Among them, the thiazoles and related heterocycles as privileged heterocycles are of special interest in the design of new drug-like molecules with various therapeutic effects, including a cardioprotective one [4,5]. Substituted thiazoles are proposed to be useful as antihypertensive, cardioprotective, antiarrhythmic, and antianginal agents which exhibit cardioselective  $\beta$ -adrenergic blocking activity [6,7].

The purpose of the project was the search for new safe and effective biologically active substances with a cardioprotective action among 1,3-thiazole derivatives. Despite a large number of publications, there is practically no information in the literature on the physical, chemical, and biological properties

of compounds bearing the combination of different heterocyclic core nuclei such as piperazine, morpholine, and 1,3-thiazole cores in one molecule. Since in current medicine there are some examples of the successful use of drugs based on these heterocycles, we considered it expedient to combine these known important structures in one molecule [8–10].

The presence of several heterocycles in the structure of the target compounds can lead either to the synergism of the biological effect or to the appearance of new pharmacological actions, especially within multifunctional compounds strategy [11,12]. In addition, in order to determine the structural and biological patterns, it was planned to introduce thiazole ring substituents with different alkyl chain lengths into the 3rd position between the nitrogen of the 1,3-thiazole, morpholine, and piperazine cycles.

## 2. Materials and Methods

### 2.1. Chemistry

All chemicals were of analytical grade, commercially available, and used without further purification. 3-Chloropentane-2,4-dione, ethyl-2-chloro-3-oxobutanoate, piperazinoethylamine, 4-methylpiperazinoamine, 3,4-dimethoxyphenylethylamine, and morpholinoethylamine were purchased from Acros Organics and used without further purification. Aryl isothiocyanates were synthesized by aromatic amines treatment using tetramethylthiuram disulfide followed by destruction of intermediate  $N_{(1)}$ -aryl- $N,N$ -dimethylthiourea under the action of concentrated HCl [13]. Asymmetric thioureas were synthesized by condensation of aryl isothiocyanates and appropriate arylamines in dioxane by known methods [14–18]. The elemental analysis of the nitrogen content was performed using the Dumas method.  $^1H$  NMR spectra and  $^{13}C$  NMR spectra were recorded in  $DMSO-d_6$  on a Varian Gemini 400 and Varian Gemini 100 MHz (Germany) spectrometers; tetramethylsilane (TMS) was used as an internal standard. LCMS spectra were recorded on a Finnigan MAT INCOS-50 using electrospray ionization (ESI) technique.

### 2.2. General Procedure for Synthesis of 2-Arylimino-1,3-Thiazoles (4a–c)

A total of 0.005 Mol of ethyl-2-chloro-3-oxobutanoate or 3-chloropentane-2,4-dione was added with stirring to a solution of 0.005 mol of appropriate asymmetric thiourea [18] in 40 mL of ethanol and heated under reflux for 2 h. After cooling, the solid that precipitated out was filtered off and crystallized from 2-propanol.

#### 2.2.1. Ethyl-2-(4-Methylphenylimino)-4-Methyl-3-(Morpholinoethyl)-2,3-Dihydro-1,3-Thiazole-5-Carboxylate Hydrochloride (4a)

Yield: 73%, m.p. = 179–182 °C.  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ : 1.20 (t, 3H,  $OCH_2CH_3$ ), 2.28 (s, 3H,  $CH_3$ ), 2.66 (s, 3H,  $CH_3$ ), 3.39 (m, 4H,  $CH_2NCH_2$ ), 3.47 (m, 2H,  $CH_2$ ), 3.90 (m, 4H,  $CH_2OCH_2$ ), 4.16 (q, 2H,  $OCH_2CH_2$ ), 4.40 (m, 2H,  $CH_2$ ), 6.94 and 7.17 (d-d, 4H, arom.,  $J = 8.1$  Hz), 11.60 (s, 1H,  $NH^+$ ).  $^{13}C$  NMR (100 MHz,  $DMSO-d_6$ )  $\delta$ : 14.1, 16.9, 20.7, 50.5, 53.1, 53.7, 61.5, 66.5, 118.0, 125.5, 129.7, 131.1, 142.7, 148.8, 165.0, 166.1. LCMS (ESI)  $m/z$  390.2 ( $M + H$ ) $^+$ . Anal. calcd. for  $C_{20}H_{28}ClN_3O_3S$ , % N 9.86. Found: % N 9.61.

#### 2.2.2. 1-[2-(Phenylimino)-4-Methyl-3-[2-(Piperazine-1-yl)Ethyl]-2,3-Dihydro-1,3-Thiazole-5-yl]Ethan-1-One Hydrochloride (4b)

Yield: 75%, m.p 194–195 °C.  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ : 2.34 (s, 3H,  $CH_3$ ), 2.65 (s, 3H,  $CH_3$ ), 3.38–3.53 (m, 10H,  $CH_2 + CH_2NCH_2 + CH_2NHCH_2$ ), 4.36 (t, 2H,  $CH_2$ ), 7.04 (d, 2H, arom.), 7.09 (t, 1H, arom.), 7.37 (d, 2H, arom.), 9.66 (s, 2H,  $NH_2^+$ ).  $^{13}C$  NMR (100 MHz,  $DMSO-d_6$ )  $\delta$ : 16.7, 26.8, 45.3, 50.7, 51.9, 53.2, 121.6, 124.4, 128.9, 142.5, 149.4, 165.6, 189.7. LCMS (ESI)  $m/z$  345.2 ( $M + H$ ) $^+$ . Anal. calcd. for  $C_{18}H_{25}ClN_4OS$ , % N 14.7. Found, %: N 14.5.

### 2.2.3. Ethyl-2-(4-Methoxyphenyl)imino]-4-Methyl-3-(4-Methylpiperazine-1-yl)-2,3-Dihydro-1,3-Thiazole-5-Carboxylate Hydrochloride (4c)

Yield: 70%, m.p. 174–176 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 1.20 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 2.71 (s, 3H, CH<sub>3</sub>), 2.86 (m, 4H, CH<sub>2</sub>NCH<sub>2</sub>), 3.12 (m, 4H, CH<sub>2</sub>NCH<sub>2</sub>), 3.50 (m, 2H, CH<sub>2</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 7.10 and 7.30 (dd, 4H, arom., J = 8.2 Hz), 11.00 (s, 1H, NH<sup>+</sup>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 14.2, 16.9, 20.8, 50.5, 52.0, 55.3, 82.0, 113.5, 114.8, 128.3, 130., 146.9, 159.5, 165.6, 188.9. LCMS (ESI) m/z 391.0 (M + H)<sup>+</sup> Anal. calcd. for C<sub>19</sub>H<sub>26</sub>ClN<sub>4</sub>O<sub>3</sub>S, % N 13,2 %. Found, %: N 13.4.

### 2.2.4. 1-[(2-[(4-Methoxyphenyl)imino]-4-Methyl-3-(4-Methylpiperazine-1-yl)-2,3-Dihydro-1,3-Thiazole-5-yl] Ethan-1-One Hydrochloride (4d)

Yield: 67%, m.p. 178–180 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 2.16 (s, 3H, CH<sub>3</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 2.74 (s, 3H, CH<sub>3</sub>), 2.86 (m, 4H, CH<sub>2</sub>NCH<sub>2</sub>), 3.12 (m, 4H, CH<sub>2</sub>NCH<sub>2</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 7.06 and 7.25 (dd, 4H, arom., J = 8.1 Hz), 10.9 (s, 1H, NH<sup>+</sup>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 14.8, 29.5, 41.6, 50.7, 51.9, 55.3, 82.0, 113.4, 114.7, 128.3, 129.6, 146.7, 159.2, 165.4, 188.7. LCMS (ESI) m/z 361.2 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>18</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>2</sub>S, % N 14,3 %. Found, %: N 14.1.

### 2.3. Synthesis of 1-[2-[(2-Methylphenyl)imino]-4-Methyl-3-[2-(3,4-Dimethoxyphenyl)ethyl]-2,3-Dihydro-1,3-Thiazole-5-yl-Ethan-1-One (5)

A total of 0.67 g (0.005 mol) of 3-chloropentane-2,4-dione was added with stirring to a solution of 1.65 g (0.005 mol) of 1-(2-methylphenyl)-3-(3,4-dimethoxyphenylethyl-1-yl)thiourea in 40 mL of ethanol and heated under reflux for 2 h. After cooling, 10% ammonia solution was added. The precipitated solid was filtered off and crystallized from 2-propanol. Yield: 65%, m.p. 102–103 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 2.17 (s, 3H, CH<sub>3</sub>), 2.25 (s, 3H, CH<sub>3</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 3.00 (t, 2H, CH<sub>2</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 4.17 (t, 2H, CH<sub>2</sub>), 6.76–7.27 (m, 7H, C<sub>4</sub>H<sub>3</sub>+C<sub>4</sub>H<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 17.0, 18.2, 26.8, 35.5, 48.5, 55.4, 55.5, 111.7, 112.0, 121.1, 123.5, 125.5, 129.2, 132.7, 136.0, 143.7, 147.3, 149.3, 149.8, 162.3, 189.7. LCMS (ESI) m/z 411.2 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S N 6.82%. Found: %: N 6.58.

### 2.4. Synthesis of Ethyl-[2-[(4-Methoxyphenyl)imino]-4-Methyl-3-(4-Methylpiperazin-1-yl)-2,3-Dihydro-1,3-Thiazole-5-Carboxylate (6)

A total of 0.82 g (0.005 mol) of ethyl-2-chloro-3-oxobutanoate was added with stirring to a solution of 1.40 g (0.005 mol) of 1-(4-methoxyphenyl)-3-(4-methylpiperazin-1-yl)thiourea in 40 mL of ethanol and boiled under reflux for 2 h. After cooling, 10% ammonia solution was added. The precipitated solid was filtered off and crystallized from 2-propanol. Yield: 68%, m.p. 131–132 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 1.26 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.13 (s, 3H, CH<sub>3</sub>), 2.17 (s, 3H, CH<sub>3</sub>), 2.40 (m, 4H, CH<sub>2</sub>NCH<sub>2</sub>), 2.56 (m, 4H, CH<sub>2</sub>NCH<sub>2</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 4.20 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 7.03 and 7.22 (dd, 4H, arom., J = 8.1 Hz). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 14.1, 16.2, 43.1, 47.9, 52.2, 55.4, 61.5, 113.7, 123.0, 143.7, 146.3, 154.8, 163.0, 166.8. LCMS (ESI) m/z 389.2 (M+H)<sup>+</sup> Anal. calcd. for C<sub>19</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub>S. N 14,3 %. Found: %: N 14.6.

### 2.5. Pharmacology

The studies were performed on mature female rats weighing 267 ± 11.2 g, which were on the standard PC "Biomodel Service" diet with free access to food and water (Ethical Committee of Institutional Animal Care and Use Committee Approval: 21/12/2018 No. 9.). All experimental studies were carried out according to the European Convention on Animals Protection (1986), the "Regulations on the Use of Animals in Biomedical Research" (1989). Before the start of the experiment, the animals were set apart without access to food and water for 1 h to standardize the stress state in experimental studies. Then, the animals were weighed and euthanized by decapitation under light ether anesthesia according to the European Convention on Animals Protection.

The cardioprotective properties of the new 1,3-thiazole derivatives were studied on the isolated rings of the thoracic aorta of laboratory rats. The target organ was removed immediately from the dead

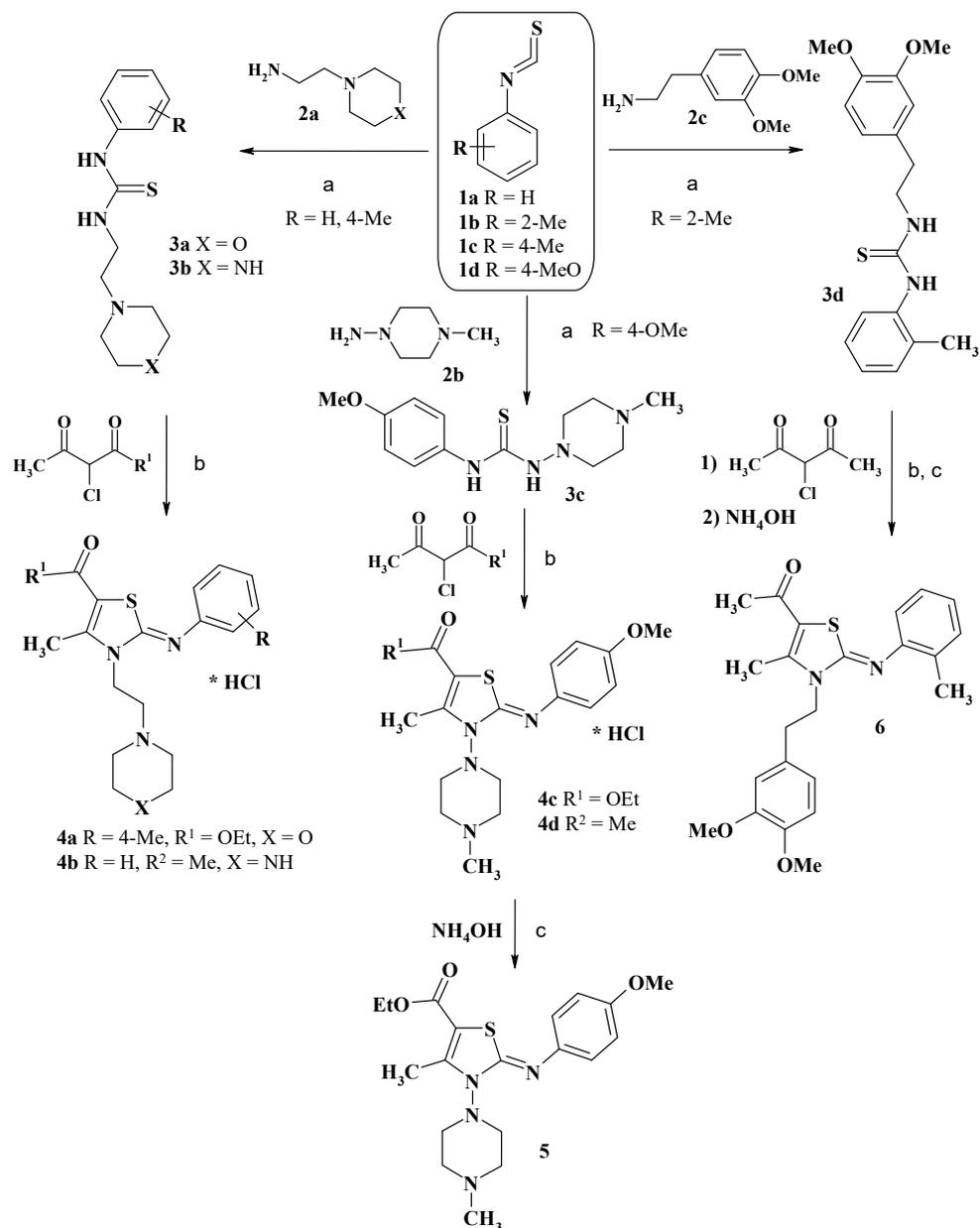
animal and was placed in Krebs solution of the following composition (in mmol/L): NaCl—32; KCl—4.7; NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O—1.4; NaHCO<sub>3</sub>—16.3; CaCl<sub>2</sub>—2.5; MgCl<sub>2</sub>·2H<sub>2</sub>O—1.05; glucose—6.5. Aeration of the solution was carried out with carbogen (gas mixture 5% CO<sub>2</sub>/95% O<sub>2</sub>) [19]. Further, the biological material was placed on a paraffinic operating table in the Krebs solution at room temperature. After fixation with hooks, the biological material was cleaned from fat and connective tissues. The smooth muscle preparations purified were cut into rings with a width of 1 mm at an angle of 45°. The isolated and purified isolated rings of the thoracic aorta of rats were secured in a flow chamber (myographic unit) on two steel hooks with a previous load of 1.5 g. A 0.5 mL chamber was perfused with Krebs solution of the following composition in mmol/L: NaCl—132; KCl—4.7; NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O—1.4; NaHCO<sub>3</sub>—16.3; CaCl<sub>2</sub>—2.5; MgCl<sub>2</sub>·2H<sub>2</sub>O—1.05; glucose—6.5, at a rate of 1.5 mL/min at a stable temperature of about 37 ± 0.5 °C. The initial tonic contraction of the isolated rings of the thoracic aorta of rats was caused by the hyper-potassium solution (KCl—60 mmol/L). The test compounds were dissolved in dimethylsulphoxide followed by diluting in Krebs solution at the examined concentration of 100 µmol/L. The force of contractile response was measured in the isometric mode using capacitive strain gauges (FTK-0.1; “Miosensor” Ltd). The contractions were recorded on a personal computer using DataTrax2 software by means of a Lab-Trax-4/16 analog-to-digital converter (World Precision Instruments). After stabilizing the isolated aortic rings for periodic stimulation using Krebs hyper-potassium solution (KCl—60 mmol/L) for 50 min (10 min stimulation using the hyper-potassium solution followed by washing with Krebs solution for 15 min, all performed twice), the test compounds were applied at the given concentration for 20 minutes. Further, a model of hypoxia was simulated by aerating Krebs solution with nitrogen for 40 min. The experiment was completed by monitoring the contractile activity of the isolated rings of the thoracic aorta by treating them with Krebs solution with phenylephrine (10<sup>-6</sup> mol/L) for 10 to 15 minutes to achieve the constriction plateau, following which, Krebs solution was perfused, and the level of relaxation was observed. The mechanogram recorded whether the isolated vascular tone changed under application of the test compounds. The normalized maximum rate of the contraction phase (V<sub>nc</sub>) was calculated for hypoxia, and the presence of any contraction in case of phenylephrine and the level of relaxation were analyzed at the end of the experiment [19–22], L-carnitine and Meldonium were chosen as reference drugs.

### 3. Results and Discussion

#### 3.1. Chemistry

The asymmetrical thioureas (**3a–d**) as starting compounds were synthesized by a known method [14–17] via reaction of aryl isothiocyanates with piperazino- and morpholinostituted arylamines, as well as 3,4-dimethoxyphenethylamine in dry dioxane [18]. Target 2-arylimino-2,3-dihydro-1,3-thiazoles were obtained via the [2+3]-cyclocondensation (Hantzsch reaction) of asymmetrical thioureas **3a–d** as S,N-binucleophiles in reactions with 3-chloropentane-2,4-dione or ethyl 2-chloro-3-oxobutanoate as equivalents of dielectrophilic synthon [C<sub>2</sub>]<sup>2+</sup>. As a result, 3-substituted 1-(2-arylimino-4-methyl-2,3-dihydro-1,3-thiazol-5-yl) ethan-1-ones (**4b**, **4d**) and ethyl-2-arylimino-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate hydrochlorides (**4a**, **4c**) were synthesized with good yields. Compounds **5** and **6** were isolated as bases by neutralizing the corresponding hydrochlorides with a 10% solution of NH<sub>4</sub>OH, see Scheme 1.

The structure of the synthesized compounds was confirmed by elemental analysis and by LCMS, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

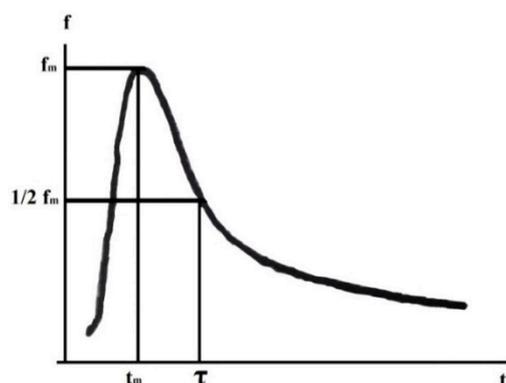


**Scheme 1.** Target 2-arylimino-2,3-dihydro-1,3-thiazoles synthesis. Reagents and conditions: (a) appropriate aryl isothiocyanate (1.0 equiv), appropriate arylamine (1.0 equiv), dioxane, r.t., 1 h [18]; (b) appropriate thiourea (1.0 equiv), 3-chloropentane-2,4-dione or ethyl-2-chloro-3-oxobutanoate (1 equiv), EtOH, reflux, 2 h, (c) appropriate hydrochloride of 2-arylimino-2,3-dihydro-1,3-thiazole (1.0 equiv), 10% NH<sub>4</sub>OH (1.0 equiv), r.t.

### 3.2. Pharmacology

Pharmacological screening has shown that the obtained substances possess cardioprotective activity. The indicator of cardioprotective activity was the normalized maximum rate of the contraction phase (V<sub>nc</sub>). The essence of the method is to standardize the analysis of the mechanogram "contraction-relaxation" of smooth muscle organs, which does not depend on the size of the isolated smooth muscle preparation used in the experiment [19].

During analysis of mechanokinetic curves, linearization of the contraction phase was done in the coordinates  $[\ln [(f_m - f) / f]; \ln t]$ , where  $f$ —instantaneous force (at time  $t$ ),  $f_m$ —maximum force,  $t$ —characteristic time, and  $n$ —logarithmic coefficient of slope of the mechanokinetic curve, see Figure 1.



**Figure 1.** Graphical representation of the course of the smooth muscles contraction and relaxation phase.

This method allows for the calculation of indicators depending on the maximum force—standardized value of the maximum contraction-rate  $V_n$  (1):

$$V_n = \pm \left( \frac{1}{f_m} \right) \left( \frac{df}{dt} \right) = \left| - \frac{(n-1)^{\frac{n-1}{n}} (n-1)^{\frac{n+1}{n}}}{4n\tau} \right| \quad (1)$$

The effect of compounds examined on the contraction of isolated aortic thoracic rings for hypoxia was analyzed using the calculated normalized maximum rate of the contraction phase ( $V_{nc}$ —from the start of the muscle preparation strain increase to the maximum), in accordance with Formula (1).

Using in vitro experiments, it was established that application of the tested compounds to isolated rings of the thoracic aorta of laboratory rats has not caused constrictor responses of the latter, and for the two compounds, the decreases in vascular tone have been inherent.

For cardioprotective drugs, the ability to influence energy processes in cardiomyocytes is of high importance. This directly depends on the rate of pathophysiologic myocardium damages development. In our experiment, we modeled the pathological state of hypoxia, in order to analyze the effect of the test compounds on the rate of hypoxic contraction development of the rings of the thoracic aorta of rats.

Based on pharmacological studies, a prospective 1-[2-(4-methoxyphenylimino)-4-methyl-3-(4-methylpiperazine-1-yl)-2,3-dihydro-1,3-thiazole-5-yl]ethan-1-one hydrochloride **4c** was identified. Compound **4c** has delayed the development of constrictor responses of isolated rings of the thoracic aorta of rats, shows a well-pronounced cardioprotective effect, and exceeds the activity of L-carnitine by 18.2% and meldonium by 12.9%, see Table 1. Compound **4b** reduced the normalized maximum rate of the contraction phase for hypoxia on a par with the drugs of comparison, that may indicate the ability of this compound to decrease in the energy potential of the cardiomyocyte damaged by hypoxia. Derivatives **4a**, **5**, and **6** also did not decrease, but accelerated by 0.5-times the normalized maximum rate of the contraction phase for hypoxia, which indicates the energy-consuming mechanism of their action, see Table 1.

Following the presented results of the pharmacological study, the cardioprotective activity of the obtained compounds depends on the nature of the substituents at positions 3 and 5 of the thiazole cycle. The cardioprotective activity decreases with an increase in the length of the aliphatic chain of substituents at position 3. The presence of alkyl radicals and piperazine fragments in the structure of the 1,3-thiazole derivatives positively affects the activity index. The replacement of the ethane-1-one fragment with carboxylate moiety at position 5 of the thiazole core resulted in a cardioprotective effect decrease.

**Table 1.** The normalized maximum rate of the contraction phase (Vnc) for hypoxia of the tested compounds.

Compound	Vnc (M ± m)
4a	0.081 ± 0.007
4b	0.035 ± 0.006
4c	0.027 ± 0.003
4d	0.085 ± 0.010
5	0.093 ± 0.012
6	0.087 ± 0.013
L-carnitine	0.033 ± 0.005
Meldonium	0.031 ± 0.004
Negative Control Value	0.062 ± 0.019

#### 4. Conclusions

In the presented paper, the series of 2-arylimino-4-methyl-2,3-dihydro-1,3-thiazoles were obtained based on the Hantzsch reaction of asymmetric thioureas as S,N-binucleophiles and 3-chloropentane-2,4-dione or ethyl 2-chloro-3-oxobutanoate as equivalents of dielectrophilic synthon [C<sub>2</sub>]<sup>2+</sup>. The structure of synthesized compounds was confirmed by LCMS, <sup>1</sup>H and <sup>13</sup>C NMR spectra. Compounds were screened for their cardioprotective activity using an in vitro model of the isolated rings of the rats' thoracic aorta. Among the tested compounds, 1-[2-(4-methoxyphenylimino)-4-methyl-3-(4-methylpiperazine-1-yl)-2,3-dihydro-1,3-thiazole-5-yl] ethan-1-onehydrochloride **4c** possessed a high activity level and had effects similar to L-carnitine and Meldonium. Thus, a new thiazole derivative as an interesting candidate for further testing and for the design of new cardioprotective agents has been identified.

**Author Contributions:** I.D. (Iryna Drapak), L.P., and S.T. conceived and designed the project and paper; I.D. (Inna Demchuk), I.D. (Iryna Drapak), and M.S. performed the synthesis of target compounds; N.S., N.D., and I.G. tested compounds for cardioprotective activity; I.D. (Iryna Drapak). and L.P. wrote the paper. All authors read and approved the final manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

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