

# The synthesis of N-(4-aryl-thiazol-2-yl)-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromides and the cardioprotective activity of (4<sup>1</sup>-methoxyphenyl-thiazol-2-yl) derivative

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## Abstract

A novel series of N-(4-aryl-thiazol-2-yl)-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine derivatives were synthesized by interaction of equimolar quantities of substituted α-bromacetophenones with thiosemicarbazide and characterized on the basis of their elemental analyses and spectral data. Study of cardioprotective activity of the all new products in comparison to levocarnitine and its synthetic analogue mildronate were carried out. Thus, specified results indicate, N-[(4<sup>1</sup>-methoxyphenyl)-thiazol-2-yl]-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromide was influenced deceleration of contractive response of smooth muscles to hypoxia 13.2% more effective than levocarnitine and 6.85% more effective than mildronate and were shown pronounced cardioprotective properties. Obtained data justifies further study of N-(4-aryl-thiazol-2-yl)-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-yl)-hydrazine derivatives as new potential cardioprotective drugs for treatment of various cardiac diseases.

## Keywords

Cardioprotective activity, Mildronate, Levocarnitine, N-(4-aryl-thiazol-2-yl)-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine derivatives

## Introduction

One of the relevant tasks in modern pharmacy is the search for new synthetic cardioprotective drugs. According to the WHO data, the mortality rate from cardiovascular diseases reaches 31% from all deaths in the world, while the mortality rate from ischemic disease and strokes is

more than half of those cases. It indicates that lethality of these diseases is on the first place that is close to tumors (Johri et al. 2014).

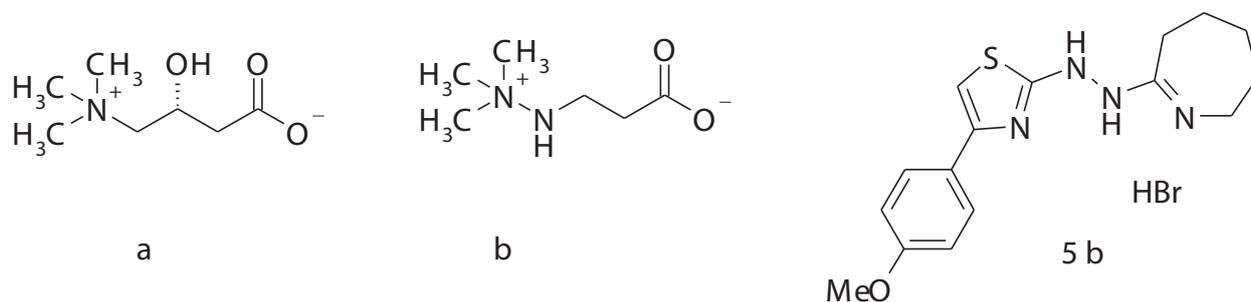
Cardiovascular pathologies are not only a medical problem, but also a social one. Annually, the state spends large sums on diagnostics and treatment of such patients,

and a high level of disability in patients with a cardiovascular pathology causes significant financial losses to both the state and the family or caretakers.

At the core of the effective therapy of ischemia, heart attacks and strokes impacts, there is a complex neurocytoprotective therapy, which relevance is associated with the increase in number of patients with acute atrophic and neurodegenerative processes caused by strokes, stenosis processes in brachiocephalic arteries, diabetes, arterial hypertension, Alzheimer disease, etc. (Dinicolantonio et al. 2013).

To correct the impact of both acute and chronic forms of cardiovascular diseases, it is important to provide patients with effective drugs.

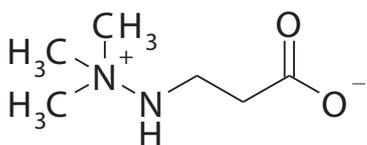
Levocarnitine is a vitamin-like compound, the main cofactor of the fatty acid metabolism (Fig.1).



**Figure 1.** Structural formulas for active components of Levocarnitine (a), Mildronate (b) and N-[4-(4'-methoxyphenyl)-thiazol-2-yl]-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromide (5 b)

This compound has the ability to carry long chain fatty acids to mitochondria where their oxidation and the synthesis of ATP occur. This drug contributes to removal of toxins and metabolites from the cytoplasm of cardiomyocytes, improves metabolic processes and accelerates reparative processes in the myocardium. It has the cardioprotective effect, contributes to reduction of ischemia in the myocardium. Levocarnitine is the only cardiometabolic drug, which can be officially used from the time of birth. However, under the effect of cardiometabolic therapy with levocarnitine a lot of side effects, such as eating disorders, risk of anorexia nervosa, allergic reactions, depression, aggression, convulsions, etc., are observed (Zeiler et al. 2016).

Mildronate (meldonium) (Fig. 2) created in the Latvian Institute of Organic Synthesis and characterized by its ability to improve the metabolism and energy supply in cells. Due to its cytoprotective properties this drug is used for the treatment of pathologies of ischemic genesis as a cardioprotective, antihypoxic, angioprotective and anti-anginal drug (Dambrova et al. 2002; Degrace et al. 2004; Sjakste et al. 2005).



**Figure 2.** Mildronate (meldonium).

It should be noted that use of mildronate may provoke disorders, such as allergic reactions (swelling, redness, rash and itching). Dyspeptic symptoms, tachycardia, agitation, reduction of arterial pressure were observed as side effects after use of this drug (Dambrova et al. 2016).

Considering the abovementioned the constant expansion of the arsenal of effective, safe cardioprotective drugs is necessary for providing the individual approach in the complex treatment of cardiac pathologies.

Earlier (Demchenko et al. 2018), we synthesized and studied the cardioprotective activity of N-[4-(4'-methoxyphenyl)-thiazol-2-yl]-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromide (5 b).

The substituted N-(4-aryl-thiazol-2-yl)-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromides (5 a-d)

draw interest as potential biologically active compounds. Obtaining of the corresponding salts under conditions of the Hantzsch reaction (Mazzone et al. 1992) and further condensation with 7-methoxy-3,4,5,6-tetrahydro-3H-azepin is the main approach to the synthesis of these compounds.

The aim of the study was to synthesize the derivatives of N-(4-aryl-thiazol-2-yl)-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromides and study the cardioprotective activity of N-[4-(4'-methoxyphenyl)-thiazol-2-yl]-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromide at the stage of the primary pharmacological screening.

## Experimental part

### Materials and methods

All solvents and reagents (from Aldrich and Acros) were used without additional purification. Control of the reaction and purity of the compounds synthesized was performed by the method of thin layer chromatography on Silufol, F<sub>254</sub>, 1×10 cm plates, eluents of the mixture, chloroform – methanol and ethyl acetate – hexane (9:1 and 1:1 v/v, respectively), using a UV-detector with the wavelength of 254 and 356 nm. Melting points were measured on a compact heating table with a PHMK 05 (VEB Analytik, Dresden) tracking device. <sup>1</sup>H NMR spectra were registered on a Bruker 300 MHz spectrometer (TMS as a standard, DMSO-d<sub>6</sub> as a solvent).

7-Methoxy-3,4,5,6-tetrahydro-2*H*-azepine **4** was obtained by alkylating caprolactam with dimethyl sulfate using the method (Granik et al. 1973) in a dry benzene. Hydrobromides of 2-hydrazino-4-arylthiazoles (**3 a-d**) were obtained by condensation of the corresponding phenacyl bromide (**1 a-d**) with thiosemicarbazide (**2**) by the method (Mazzone et al. 1992).

In the NMR spectra of compounds (**5 a-d**) the signals of the methylene groups of the azepine ring were registered in the region of 1.55–3.49 ppm. It should be noted that the methylene group in position 7 of the azepine heterocycle was registered in the weakest field at 3.48–3.49 ppm relative to other methylene groups of the ring. The proton of the thiazole ring in position 5 of the heterocyclic system can be identified among other aromatic protons in the region of 7.31–7.58 ppm, respectively. It should be mentioned that for compounds (**5 a-c**) there was a correlation between the chemical shifts of protons in position 5 of the system and the electronic effects of the benzene ring *para*-substituents in position 4 of the thiazole ring ( $\sigma$ -*para* of the Hammett constants (Gordon and Ford, 1976). Thus, a single-proton 5H singlet was registered at 7.31 ppm for compound **5 b** with an electron-donating group ( $-\text{OCH}_3$ ,  $\sigma$ -*para* = -0.28). When the electronic nature of the substituent changed to an electron-acceptor in compound **5 c** ( $-\text{Cl}$ ,  $\sigma$ -*para* = +0.22) the single-proton singlet shifted to a weaker field at 7.58 ppm. Signals of two protons of the hydrazine fragment of molecules ( $-\text{NHNH}-$ ) were registered in the region of 9.95–10.3 ppm. It should be noted that there was a single-proton singlet at 11.7 ppm the NMR spectra of all compounds (**5 a-d**). This fact indicates that the nitrogen atom of the azepine ring is strongly protonated with hydrobromic acid and that the tautomeric form of quaternary salts ( $=\text{NH}^+$ )(Br<sup>-</sup>) (**6 a-d**) exists in the solution.

#### Synthesis of *N*-(4-phenyl-thiazol-2-yl)-*N*<sup>1</sup>-(4,5,6,7-tetrahydro-3*H*-azepin-2-yl)hydrazin hydrobromide (**5 a**)

To solution of 0.91 g (0.01 mol) thiosemicarbazide **2** in 60 ml ethanol 1.99 g (0.01 mol)  $\alpha$ -bromoacetophenone **1 a** was added. The reaction mixture was refluxed for 1 hour. After cooling, 1.40 g (0.011 mol) of 7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine **4** was added to reaction mixture and held for 24 hours at 20 °C. The solvent was evaporated to volume of 10 ml. The precipitate was filtered off and dried. Yield 2.39 g (65%). M.p.=179–180 °C. Anal. Calcd. for  $\text{C}_{15}\text{H}_{19}\text{BrN}_4\text{S}$ . %: C=49.1 H=5.21 N=15.2 Br=21.8. Found, %: C=49.5 H=5.37 N=15.3 Br=20.6. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, TMS),  $\delta$  (ppm): 1.56 (m, 2H, 5-CH<sub>2</sub>), 1.77 (m, 4H, 4,6-CH<sub>2</sub>CH<sub>2</sub>), 2.82 (m, 2H, 3-CH<sub>2</sub>), 3.49 (m, 2H, 7-CH<sub>2</sub>), 7.30–7.87 (m, 5H, C<sub>6</sub>H<sub>5</sub>), 7.51 (s, 1H, 5-H), 10.0 (s, 1H, NH), 10.3 (s, 1H, NH), 11.7 (s, 1H, NH).

#### Synthesis of *N*-[(4<sup>1</sup>-methoxyphenyl)-thiazol-2-yl]-*N*<sup>1</sup>-(4,5,6,7-tetrahydro-3*H*-azepin-azepin-2-yl)-hydrazine hydrobromide (**5 b**)

To solution of 0.91 g (0.01 mol) thiosemicarbazide **2** in 60 ml ethanol 2.29 g (0.01 mol)  $\alpha$ -bromo-4-

methoxyacetophenone **1 b** was added. The reaction mixture was refluxed for 1 hour. After cooling, 1.40 g (0.011 mol) of 7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine **4** was added to reaction mixture and held for 24 hours at 20 °C. The solvent was evaporated to volume of 10 ml. The precipitate was filtered off and dried. Yield 2.82 g (71%). M.p.=171–172 °C. Anal. Calcd. for  $\text{C}_{16}\text{H}_{21}\text{BrN}_4\text{OS}$ . %: C=48.4 H=5.33 N=14.1 S=8.07 Br=20.1. Found, %: C=48.8 H=5.4 N=14.3 S=8.14 Br=20.4. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, TMS),  $\delta$  (ppm): 1.56 (m, 2H, 5-CH<sub>2</sub>), 1.77 (m, 4H, 4,6-CH<sub>2</sub>CH<sub>2</sub>), 2.81 (m, 2H, 3-CH<sub>2</sub>), 3.49 (m, 2H, 7-CH<sub>2</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 6.98 and 7.78 (d-d, 4H, C<sub>6</sub>H<sub>4</sub>), 7.31 (s, 1H, 5-H), 9.95 (s, 1H, NH), 10.2 (s, 1H, NH), 11.7 (s, 1H, NH).

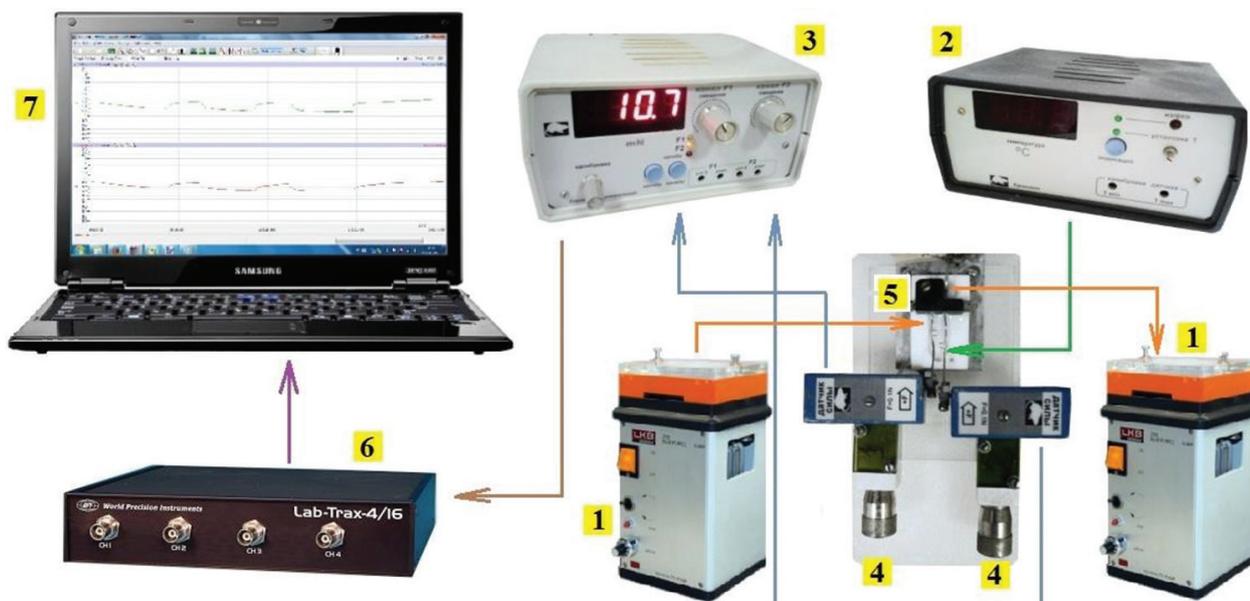
#### Synthesis of *N*-[(4<sup>1</sup>-chlorophenyl)-thiazol-2-yl]-*N*<sup>1</sup>-(4,5,6,7-tetrahydro-3*H*-azepin-2-yl)-hydrazine hydrobromide (**5 c**)

To solution of 0.91 g (0.01 mol) thiosemicarbazide **2** in 60 ml ethanol 2.33 g (0.01 mol)  $\alpha$ -bromo-4-chloroacetophenone **1 c** was added. The reaction mixture was refluxed for 1 hour. After cooling, 1.40 g (0.011 mol) of 7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine **4** was added to reaction mixture and held for 24 hours at 20 °C. The solvent was evaporated to volume of 10 ml. The precipitate was filtered off and dried. Yield 3.01 g (75%). M.p. = 233–234 °C. Anal. Calcd. for  $\text{C}_{15}\text{H}_{18}\text{BrClN}_4\text{S}$ . %: C=44.8 H=4.52 N=13.9 S=7.98 Cl=8.82 Br=19.89. Found, %: C=45.1 H=4.81 N=14.1 S=8.28 Cl=8.98 Br=20.03. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, TMS),  $\delta$  (ppm): 1.55 (m, 2H, 5-CH<sub>2</sub>), 1.77 (m, 4H, 4,6-CH<sub>2</sub>CH<sub>2</sub>), 2.80 (m, 2H, 3-CH<sub>2</sub>), 3.48 (m, 2H, 7-CH<sub>2</sub>), 7.48 and 7.87 (d-d, 4H, C<sub>6</sub>H<sub>4</sub>), 7.58 (s, 1H, 5-H), 10.0 (s, 1H, NH), 10.2 (s, 1H, NH), 11.7 (s, 1H, NH).

#### Synthesis of *N*-[4-(2,3-dihydro-benzo[1,4]dioxan-6-yl)-thiazol-2-yl]-*N*<sup>1</sup>-(4,5,6,7-tetrahydro-3*H*-azepin-2-yl)-hydrazine hydrobromide (**5 d**)

To solution of 0.91 g (0.01 mol) thiosemicarbazide **2** in 60 ml ethanol 2.57 g (0.01 mol) 2-bromo-1-(2,3-dihydro-benzo[1,4]dioxan-6-yl)ethanone **1 d** was added. The reaction mixture was refluxed for 1 hour. After cooling, 1.40 g (0.011 mol) of 7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine **4** was added to reaction mixture and held for 24 hours at 20 °C. The solvent was evaporated to volume of 10 ml. The precipitate was filtered off and dried. Yield 2.98 g (70%). M.p.=207–207 °C. Anal. Calcd. for  $\text{C}_{17}\text{H}_{21}\text{BrN}_4\text{O}_2\text{S}$ . %: C=48.0 H=4.98 N=13.2 S=7.54 Br=18.8. Found, %: C=48.4 H=5.12 N=13.3 S=7.77 Br=18.5. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, TMS),  $\delta$  (ppm): 1.55 (m, 2H, 5-CH<sub>2</sub>), 1.76 (m, 4H, 4,6-CH<sub>2</sub>CH<sub>2</sub>), 2.82 (m, 2H, 3-CH<sub>2</sub>), 3.48 (m, 2H, 7-CH<sub>2</sub>), 4.26 (s, 4H,  $-\text{OCH}_2\text{CH}_2\text{O}-$ ), 6.88–7.34 (m, 3H, C<sub>6</sub>H<sub>3</sub>), 7.37 (s, 1H, 5-H), 9.98 (s, 1H, NH), 10.2 (s, 1H, NH), 11.7 (s, 1H, NH).

The cardioprotective activity of *N*-[4-(4<sup>1</sup>-methoxyphenyl)-thiazol-2-yl]-*N*<sup>1</sup>-(4,5,6,7-tetrahydro-3*H*-azepin-2-yl)-hydrazine hydrobromide (**5 b**) was tested *in vitro* on the isolated rings of the thoracic aorta of laboratory rats



**Figure 3.** Smooth muscle preparations miographic study methodic scheme, where: 1 peristaltic pump 2 thermostat 3 amplifier 4 Capacitive tensometric sensor 5 work chamber (heated with thermostat) 6 analog-to-digital converter 7 personal computer.

(Stefanov 2001; Blattner et al. 1983; Drapak et al. 2019). The studies were conducted on rats bred in the vivarium of the Institute of Pharmacology and Toxicology of the NAMS of Ukraine. The animals were kept on a standard diet, received food and water *ad libitum*.

The studies of the cardioprotective activity of N-[4-(4'-methoxyphenyl)-thiazol-2-yl]-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)hydrazine hydrobromide (**5 b**) was conducted *in vitro* by the following method (Fig. 3). The separated and cleaned isolated rings of the thoracic aorta of rats were fixed in a flow chamber (a myographic device is depicted on pic.1) on two steel nuts with previous load of 1.5 g. The chamber with a volume of 0.5 ml was perfused with the Krebs solution (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; Mg-Cl<sub>2</sub>·2H<sub>2</sub>O – 5; glucose – 6.5) at speed of 1.5 ml/min at stable temperature of 37±0.5 °C.

The output tonic contraction of the isolated rings of the thoracic aorta of rats was induced by the hyperpotassium (KCl 60 mmol/l) solution. The test compounds were dissolved in dimethylsulphoxide with the subsequent dilution in the Krebs solution to the concentration of 100 µmol/l.

The power of the contraction reaction was measured in the isometric mode using capacitive tensometric sensors (FTK-0.1). Contractions were recorded on a personal computer, with the DataTrax2 program using a Lab-Trax-4/16 analog-to-digital converter (World Precision Instruments).

After stabilizing the isolated rings of the thoracic aorta in the periodic stimulation with the hyperpotassium solution (KCl 60 mmol/l) for 50 min (2 times 10 min each) and stimulation with the hyperpotassium solution with the subsequent rinsing in the Krebs solution for 15 min the application of the test compounds in the concentra-

tion specified was conducted for 20 min. Then, model of hypoxia was simulated by aeration of the Krebs solution with nitrogen for 40 min.

The experiment was completed by monitoring the contractive activity of the isolated rings of the thoracic aorta, acting on them with the Krebs solution with phenylephrine (10–6 mol/l) for 10–15 min until achieving the constriction plateau, after that the Krebs solution was perfused, and the level of relaxation was observed.

Changes in the tonus of isolated vessels when applying the compounds studied were registered on the mechnogram, the standardized maximum speed of the contraction phase (V<sub>nc</sub>) to hypoxia was calculated; the presence of contractions under the action of phenylephrine and the level of relaxation at the end of the experiment were analyzed (Burdyga ThV and Kosterin SA 1991).

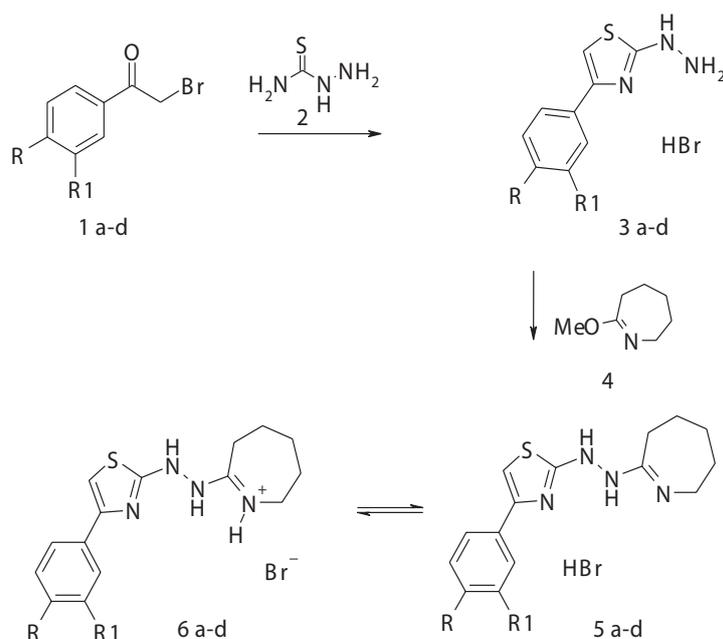
## Results and discussion

### Chemistry

The test compounds – N-(4-aryl-thiazol-2-yl)-N<sup>1</sup>-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromides (**5 a–d**) were synthesized at the Department of Medicinal Chemistry of the Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences (Fig. 1, Scheme 1).

The test compounds (**5 a–d**) were synthesized according to Scheme 1.

The efficiency of the compounds studied was compared to the negative control and the reference drugs – Mildronate and Levocarnitine (Table 1).



**Scheme 1.** Synthesis of N-(4-aryl-thiazol-2-yl)-N¹-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromides (5 a-d). Where: **1, 3, 5: a)** R=R<sub>1</sub>=H **b)** R=OCH<sub>3</sub>, R<sub>1</sub>=H; **c)** R=Cl, R<sub>1</sub>=H; **d)** RR<sub>1</sub>=-OCH<sub>2</sub>CH<sub>2</sub>O-.

**Table 1.** Standardized maximum speed of contraction (Vnc) to hypoxia of compound **5 b** and comparative drugs.

Nº	Substance	Vnc (M±m)
1	Control	0.0624 ± 0.0193
2	Levocarnitine	0.0329 ± 0.0052
3	Mildronate	0.0306 ± 0.0048
4	<b>5 b</b>	0.0285 ± 0.0018

During the studies of changes in the standardized maximum speed of the contraction phase on hypoxia the reference drugs almost similarly reduced the parameter studied compared to the negative control: Levocarnitin – by 1.90 times, Mildronate – by 2.04 times. At the same time, compound **5 b** reduced by 2.19 times, or 13.2 % more effectively affected deceleration of the contracture response of smooth muscles to hypoxia compared to Levocarnitine and 6.85 % compared to Mildronate.

Thus, the results indicate that N-[4-(4<sup>1</sup>-methoxyphenyl)-thiazol-2-yl]-N¹-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromide exhibits cardioprotective

properties. This suggests the possibility of creation of new cardioprotective drugs for the treatment of various heart diseases on its basis.

## Conclusion

New derivatives of N-[4-aryl-thiazol-2-yl]-N¹-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromides have been synthesized by the reaction of 7-methoxy-3,4,5,6-tetrahydro-2H-azepine with the corresponding 2-hydrazino-4-arylthiazol hydrobromides with the yield of 65–55%.

N-[(4<sup>1</sup>-methoxyphenyl)-thiazol-2-yl]-N¹-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine hydrobromide has an effect on slowing the contractile response of smooth muscles to hypoxia; thus, it has been found to be more effective than levocarnitine by 13.2% and than mildronate by 6.85%.

The data obtained substantiates the further study of N-(4-aryl-thiazol-2-yl)-N¹-(4,5,6,7-tetrahydro-3H-azepin-2-yl)-hydrazine derivatives as new potential cardioprotective drugs for the treatment of various cardiac diseases.

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