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Research Article

Search for angiotensin II receptor antagonists among 4-aryl-n-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine derivatives

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Abstract

The **aim** of study was to find potential antihypertensive and cardiotropic drugs among new 4-aryl-N-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imines.

Materials and methods: The target compounds were synthesized by condensation asymmetrical substituted thioureas with α-bromo-4-R_1-acetophenones in ethanol medium. The structure and purity of the compounds synthesized were confirmed by ^{1}H, ^{13}C NMR-spectroscopy and elemental analysis. Docking studies of synthesized compounds to the active site of angiotensin receptor II (PDB ID: 3R8A) were performed in order to find its potential inhibitors and to select promising compounds for experimental screening. Pharmacological studies of the influence on the cardiovascular system were performed.

Results: The results of docking studies indicate a high affinity of all tested substances to the selected biotarget. The thermodynamic probability of binding of synthesized substances to protein 3R8A was confirmed by negative values of scoring functions. Hydrobromide of 4-(4-methoxyphenyl)-N-phenyl-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine **3(1)** and hydrobrmide of 4-(4-methoxyphenyl)-N-(4-bromphenyl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine **3(3)**, which have the highest negative values of scoring functions, are recommended for *in vivo* pharmacological studies. Based on a complete analysis of the geometric location of the synthesized compounds (ligands) in the active site of the angiotensin II receptor, it was found that the complexes are formed with the involvement of Nitrogen atom of imino group, the 1,3-thiazole ring, the phenyl and alkyl moieties of the molecule form hydrogen bonds, intermolecular electrostatic and donor-acceptor interactions. The conducted pharmacological studies of the influence on the cardiovascular system have allowed to confirm the presence of antihypertensive effect inherent in compounds of this series (except for compound **3(2)**). The most effective antihypertensive effect, which is similar in duration and strength of the effect of valsartan, was the effect of compound **3(5)**.

Conclusions: In order to expand the arsenal of biologically active substances of cardiotropic action a systematic series of new 4-aryl-N-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine derivatives were synthesized. The structure and purity of the compounds synthesized were confirmed by ^{1}H, ^{13}C NMR-spectroscopy and elemental analysis. Based on the results of docking studies using Autodock 4.2.6 software, selected compounds with the best affinity for protein biomes (PDB codes: 3R8A) are promising for

experimental studies of hypotensive and cardiotropic activity. The most effective antihypertensive effect, which is similar in duration and strength of the effect of valsartan, was the effect of compound **3(5)**. A comparative analysis of the results of molecular docking and *in vivo* results suggests that there is a positive correlation between scoring protein inhibition and experimental data.

Keywords

synthesis, 4-aryl-N-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine derivatives, molecular docking, angiotensin receptor II antagonists

Introduction

Despite the progress of medicine in the treatment of cardiovascular diseases, they hold leading positions in the structure of morbidity, disability and mortality in the world (Schmieder et al. 2007). An important aspect of optimizing the search for new medical substances is the development of new original cost-effective methods of synthesis, the establishment of regularities of the relationship between the chemical structure and biological activity. This makes it possible to create a theoretical foundation for the development of directed synthesis of new biologically active substances and allows to avoid total pharmacological screening (Sachdeva S and Gupta S 2013, Makam et al. 2013, Siddiqui N and Ahsan W 2010, Abdel-Maksoud et al. 2015, Tehrani et al. 2014). New biologically active substances with antihypertensive and cardiotropic activity among the 1,3-thiazole derivatives were found recently (Perekhoda et al. 2017, Li-Min Duan et al. 2014, Drapak et al. 2019). Continuing research in this direction, we have modified the 1,3-thiazole ring by introducing pharmacophores, which potentially may affect the manifestation of the substance of cardiotropic activity.

To achieve this **aim** we combine in one molecule such active scaffolds as 2-R-phenyliminothiazole and prop-2-en.

Experimental part. Materials and methods

General method of synthesis of 4-aryl-N-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine derivatives

Hydrobrmides of 4-aryl-N-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine **3(1–7)** obtained by boiling in ethanol of equimolar amounts of asymmetric thiourea derivatives with α-bromo-4-R_1-acetophenones for 3 hours.

Hydrobromide of 4-(4-methoxyphenyl)-N-phenyl-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine 3(1)

Yield 82%, mp 190–192 °C (ethanol). ^{1}H NMR (400 MHz, DMSO-d6) δ: 3.82 (s, 3H, OCH_3), 4.68 (m, 2H, $\underline{CH_2}$–CH=CH_2) 4.87–5.26 (m, 2H, CH_2–CH=$\underline{CH_2}$), 5.89 (m, 2H, CH_2–$\underline{CH}$=CH_2), 7.02 (s,1H, thiazol), 7.10 and 7.49 (d-d, 4H, C_6H_4, J=8.8 Hz), 7.05 - 7.46 (m, 5H, C_6H_5). ^{13}C NMR (100 MHz, DMSO-d6) δ: 51.3, 55.4, 115.0, 115.2, 121.6, 122.9, 126.5, 127.8, 128.9, 131.3, 136.0, 148.9, 150.3, 152.6, 158.5. Anal. Calcd for $C_{19}H_{19}BrN_2OS$, % Br 19.8; N 6.94. Found, %: Br 19.6; N 6.82.

Hydrobromide of 4-(4-methoxyphenyl)-N-(2-methylphenyl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine 3(2)

Yield 85%, mp 212–214 °C (propanol-2). ^{1}H NMR (400 MHz, DMSO-d6) δ: 2.27 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.71 (m, 2H, $\underline{CH_2}$–CH=CH_2) 4.99–5.33 (m, 2H, CH_2–CH=$\underline{CH_2}$), 5.91 (m, 1H, CH_2–$\underline{CH}$=CH_2), 9.98 (s,1H, thiazol), 7.11 and 7.46 (d-d, 4H, C_6H_4, J=8.8 Hz), 7.39 - 7.43 (m, 4H, C_6H_4). ^{13}C NMR (100 MHz, DMSO-d6) δ: 18.2, 51.2, 55.3, 115.0, 115.1, 120.4, 123.5, 125.5, 126.6, 127.7, 129.2, 131.4, 135.3, 135.9, 148.8, 150.0, 152.4, 158.6. Anal. Calcd for $C_{20}H_{21}BrN_2OS$, % Br 19.1; N 6.71. Found, %: Br 19.3; N 6.85.

Hydrobromide of 4-(4-methoxyphenyl)-N-(4-bromphenyl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine 3(3)

Yield 87%, mp 216–218 °C (propanol-2). ^{1}H NMR (400 MHz, DMSO-d6) δ: 3.83 (s, 3H, OCH_3), 4.63 (m, 2H, $\underline{CH_2}$–CH= CH_2), 4.94–5.24 (m, 2H, CH_2–CH= $\underline{CH_2}$), 5.87 (m, 1H, CH_2–$\underline{CH}$= CH_2), 6.87 (s,1H, thiazol), 7.09 and 7.42 (d-d, 4H, C_6H_4, J=8.7 Hz), 7.35 and 7.71 (d-d, 4H, C_6H_4, J=8.4 Hz). ^{13}C NMR (100 MHz, DMSO-d6) δ: 51.1, 55.4, 114.9, 115.1, 116.0, 124.7, 126.5, 127.8, 130.0, 136.0, 148.9, 151.0, 152.6, 158.5. Anal. Calcd for $C_{19}H_{18}Br_2N_2OS$, % Br 33.1; N 5.81. Found, %: Br 29.8; N 5.76.

Hydrobromide of 4-(3-methoxyphenyl)-N-(4-methylphenyl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine 3(4)

Yield 85%, mp 212–214 °C (propanol-2). ^{1}H NMR (400 MHz, DMSO-d6) δ: 2.36 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.67 (m, 2H, $\underline{CH_2}$–CH=CH_2) 4.95–5.34 (m, 2H, CH_2–CH=$\underline{CH_2}$), 5.89 (m, 1H, CH_2–$\underline{CH}$=CH_2), 7.00 (s,1H, thiazol), 7.05–7.54 (m, 8H, arom. H). ^{13}C NMR (100 MHz, DMSO-d6) δ: 20.7, 51.3, 55.3, 112.8, 115.0, 115.9, 124.4, 124.6, 126.5, 129.7, 131.1, 132.2, 135.9, 136.8, 149.5, 149.8, 152.6, 162.3. Anal. Calcd for $C_{20}H_{21}BrN_2OS$, % Br 19.1; N 6.71. Found, %: Br 18.9; N 6.67.

Hydrobromide of 4-(4-bromophenyl)-N-[3-(trifluoromethyl)phenyl]-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine 3(5)

Yield 88%, mp 196–198 °C (ethanol). ^{1}H NMR (400 MHz, DMSO-d6) δ: 4.71 (m, 2H, $\underline{CH_2}$–CH=CH_2) 5.03–5.41 (m, 2H, CH_2–CH= $\underline{CH_2}$), 5.93 (m, 1H, CH_2–$\underline{CH}$=CH_2), 7.09 (s,1H, thiazol), 7.25–7.68 (m, 8H, arom. H). ^{13}C NMR (100 MHz, DMSO-d6) δ: 53.3, 113.1, 115.0, 117.7, 120.2, 120.6, 121.6, 122.5, 122.7, 124.5, 128.8, 130.5, 132.6, 133.2, 134.8, 148.9, 151.5, 151.7, 159.1. Anal. Calcd for $C_{19}H_{15}Br_2F_3N_2S$, % N 5.38. Found, %: N 5.47.

Hydrobromide of N,4-bis(4-bromophenyl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine 3(6)

Yield 72%, mp 190–192 °C (ethanol). ^{1}H NMR (400 MHz, DMSO-d6) δ: 4.62 (m, 2H, $\underline{CH_2}$–CH= CH_2), 4.94–5.23 (m, 2H, CH_2–CH=$\underline{CH_2}$), 5.86 (m, 1H, CH_2–$\underline{CH}$=CH_2), 6.95 (s,1H, thiazol), 7.32 and 7.69 (d-d, 4H, C_6H_4, J=8.1 Hz), 7.45 and 7.76 (d-d, 4H, C_6H_4, J=8.4 Hz). ^{13}C NMR (100 MHz, DMSO-d6) δ: 53.3, 114.8, 115.1, 117.7, 120.6, 124.7, 128.8, 132.0, 132.6, 133.2, 134.8, 151.0, 159.1. Anal. Calcd for $C_{18}H_{15}Br_3N_2S$, % Br 45.1; N 5.27. Found, %: Br 44.8; N 5.36.

Hydrobromide of 4-(2,4-dichlorophenyl)-N-(4-methylphenyl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine 3(7)

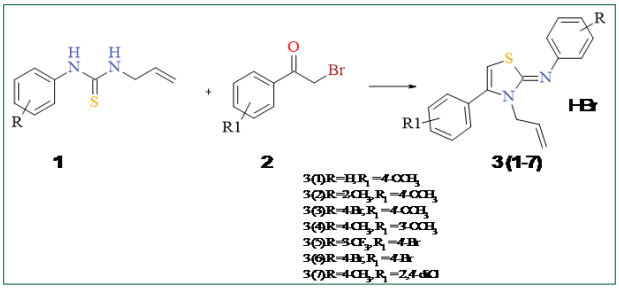
Yield 86%, mp 194–196 °C (ethanol). ^{1}H NMR (400 MHz, DMSO-d6) δ: 2.37 (s, 3H, CH_3), 4.61 (m, 2H, $\underline{CH_2}$–CH=CH_2) 4.85–5.21 (m, 2H, CH_2–CH=$\underline{CH_2}$), 5.78 (m, 1H, CH_2–$\underline{CH}$=CH_2), 7.98 (s,1H, thiazol), 7.12–7.39 (m, 7H, arom. H). ^{13}C NMR (100 MHz, DMSO-d6) δ: 20.6, 53.3, 115.0, 118.4, 124.6, 128.0, 129.7, 130.2, 131.1, 131.5, 133.0, 134.8, 135.3, 136.0, 143.9, 149.5, 159.1. Anal. Calcd for $C_{19}H_{17}Cl_2N_2S$, %: N 6.14. Found, %: N 6.27.

All reagents, and solvents that were used in the work were purchased from Acros Organics and used without further purification. Melting points of synthesized compounds compounds were determined by Kofler method. Elemental analysis of Nitrogen content was carried out by Dumas method. ^{1}H, ^{13}C NMR spectra were recorded on Varian Gemini 400 and 100 MHz in DMSO-d6 using tetramethylsilane (TMS) as an internal standard. For the receptor-based flexible docking the software package Autodock 4.2.6 was used (Autodock software package http://autodock.scrips.edu). Preparation of ligands was performed using such programs as Vega ZZ (command line) and MGL Tools 1.5.617 (MGL Tools software package, http://mgltools.scrips.edu). For calculations in Autodock 4.2.6 program the input data for the receptor and ligands were converted in a special format PDBQT. The PDBQT file creation, calculation of torsion angles and removal of hydrogen atoms in non-polar atoms for the ligands studied were performed using Vega ZZ program (command line). As a biological target for docking the active site of the macromolecule from Protein Data Bank (PDB) of angiotensin receptor II (PDB ID: 3R8A) (Casimiro-Garcia et al. 2011). The receptor maps were prepared in MGL Tools and AutoGrid programs. From PDB file ID: 3R8A water molecules, ions and ligands were removed. The following parameters of docking were determined: the translational motion step was equal to 2 Å, the quaternion angle – 50°, the torsion angle – 50°. The torsion degree of freedom and the coefficient were 2 and 0.274, respectively; the cluster tolerance – 2 Å; the external lattice energy– 1000, the maximal initial energy – 0, the maximal number of attempts – 10 000; the number of structures in the population – 300, the maximal number of stages of energy evaluation – 850 000, the maximal number of generations – 27 000, the number of structures, which pass to the next generation – 1, the level of gene mutation – 0.02, the level of crossover – 0.8, the way of crossover – arithmetic. The α-parameter of Gaussian distribution was equal to 0, and β-parameter of Gaussian distribution – 1; the number of iterations of the Lamarckian genetic algorithm – 50 for each ligand. Visual analysis of the complexes of compounds from the active site of angiotensin receptor II (PDB ID: 3R8A) was performed using Discovery Studio Visualizer 4.0 program (Discovery Studio Visualizer software package, http://accelrys.com).

Results and discussion

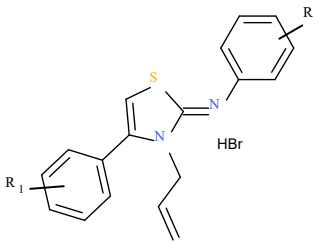
Asymmetric thioureas as starting compounds were synthesized by the interaction of R-phenylisothiocyanates and propan-3-amine in a dry dioxane medium (Taha et al. 2015). The synthesis of R-phenylisothiocyanates was carried out by treating aromatic amines with tetramethylthiuramdisulfide with the subsequent destruction of the intermediate N(1)-aryl-N,N-dimethylthiourea product under the action of concentrated HCl (Demchenko et al. 2005). α-Bromo-4-R^1-acetophenones ***2*** were obtained by bromination of R^1-acetophenones (Yeromina et al. 2016).

New series of hydrobromides of 4-aryl-N-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine **3(1–7)** were synthesized by the interaction of asymmetric thiourea derivatives ***1*** and α-bromo-4-R^1-acetophenones ***2*** in equimolar amounts by boiling in ethanol for 3 hours.



The target compounds - hydrobromides of 4-aryl-N-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine **3(1–7)** are white and light yellow crystalline substances soluble in water, methanol, ethanol, propanol-2, slightly soluble in heptane, insoluble in chloroform.

Table 1. Values of scoring functions of 1,3-thiazole new derivatives in complex with angiotensin receptor II.

Compound	Formula	R	R^1	EDoc kcal/mol
3(1)		H	4'-OCH_3	-8.59
3(2)		2-CH_3	4'-OCH_3	-8.46
3(3)		4-Br	4'-OCH_3	-8.56
3(4)		4-CH_3	3'-OCH_3	-8.48
3(5)		3-CF_3	4'-Br	-8.49
3(6)		4-Br	4'-Br	-8.45
3(7)		4-CH_3	2',4'-Cl	-8.42

The structure of the compounds synthesized was confirmed by the complex use of modern physico-chemical methods of analysis: ^1H and ^{13}C NMR-spectroscopy, elemental analysis.

In order to optimize pharmacological screening and substantiate the feasibility of experimental screening for cardiotropic activity, docking studies were conducted. Docking studies nowadays are used for dissolving of different tasks. We carried out docking investigations with the purpose of selection of compounds for *in vivo* investigation. The use of *in silico* methods allows to keep laboratory animals in the absence of an affinity for potential biotargets (Drapak at al. 2018).

As a result of the conducted molecular docking, the scoring function values for the investigated substances were calculated. Scoring functions values determine the free energy of binding a specific ligand conformational position and allow to assess the stability of the complexes formed between the ligands and the corresponding receptors, and predict the ability of the synthesized compounds to block the angiotensin receptor II.

The value of the calculated scoring functions for the complexes formed by the synthesized molecules and the angiotensin II receptor are shown in Table 1.

Thus, it can be assumed that the antagonistic properties of the synthesized compounds relative to the angiotensin II receptor can be realized by forming complexes between them, the stability of which is provided mainly due to the energetically favorable geometric location of the ligands in the active center of this acceptor, the formation of hydrogen bonds between them, intermolecular electrostatic and donor-acceptor interactions. As a consequence, the thermodynamic probability of such binding is confirmed by the negative values of the scoring functions.

Substances with the highest negative values of scoring functions among the tested compounds were found (Table 1).

Thus compound **3 (1)** (EDoc = -8,59 kcal/mol) forms a complex with the angiotensin II receptor due to the formation of a hydrogen bond between the Oxygen atom of the methoxy group and the amino acid residue of glutamine Glu343, intermolecular pi-cation interaction between the phenyl moiety of the molecule and the amino acid residue of arginine Arg288. The complex between the receptor and molecule formed by pi-sigma interactions between the 1,3-thiazole cycle and the leucine residue Leu330. Additionally, the complex is stabilized by pi-pi, pi-Alk, Alk-Alk interactions between the phenyl moieties of the molecule, the allyl fragment, and the 1,3-thiazole ring with the amino acid residues of Phe285, Cys285, Val339, Met364, Arg288 and Leu333 (Figs 1, 2).

The hydrogen bond and the pi-sulfur interaction between the Nitrogen atom of the imino group and the phenyl moiety of the molecule with the cysteine residues of Cys285 contribute to the formation of the complex of compound **3(3)** (EDoc = -8,5600 kcal/mol) and the biotarget. Pi-sigma interactions occur between the phenyl moieties of the test compound with the residues of Leu330 and Ile281. The phenyl and allyl moieties, the 1,3-thiazole ring, the Bromo atom with the corresponding amino acid residues are involved in the formation of Alk and pi-Alk interactions (Figs 3, 4).

The results of the studies indicate a high affinity of the test compounds to the active site of angiotensin receptor II.

1,3-Thiazole may be considered as a perspective scaffold for the formation of combinatorial libraries of poten-

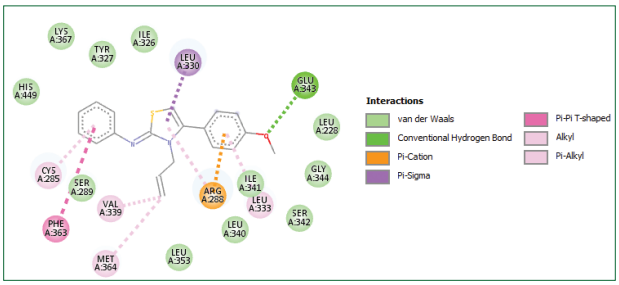


Figure 1. Diagram of the interaction of the ligand in complex with the angiotensin receptor II (PDB ID: 3R8A) for hydrobromide of 4-(4-methoxyphenyl)-N-phenyl-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine **3(1)**.

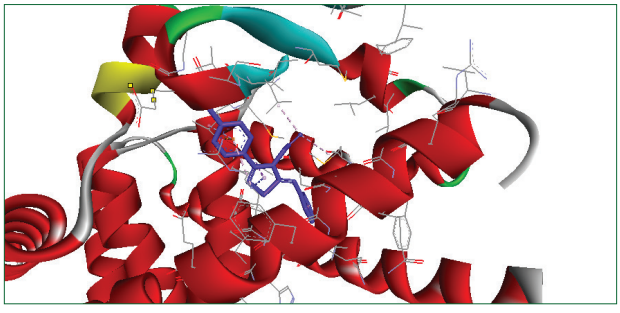


Figure 2. Superposition of molecule of the compound **3(1)** hydrobromide of 4-(4-methoxyphenyl)-N-phenyl-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine (blue) in the active site of the angiotensin receptor II (PDB ID: 3R8A).

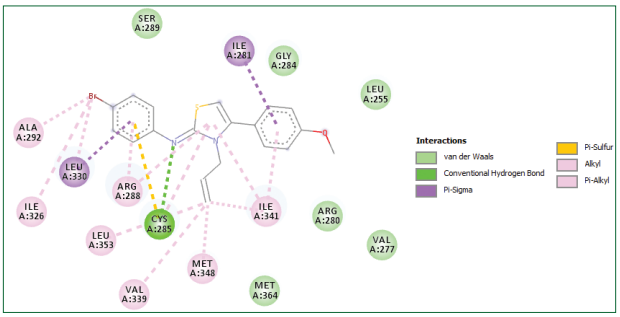


Figure 3. Diagram of the interaction of the ligand in complex with the angiotensin receptor II (PDB ID: 3R8A) for hydrobromide of 4-(4-methoxyphenyl)-N-(4-bromphenyl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine **3(3)**.

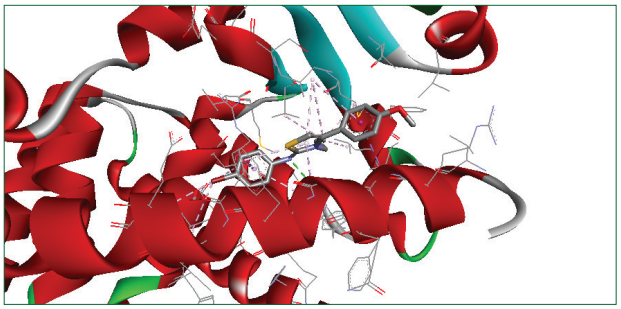


Figure 4. Superposition of molecule of the compound **3(3)** hydrobromide of 4-(4-methoxyphenyl)-N-(4-bromphenyl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine (grey) in the active site of the angiotensin receptor II (PDB ID: 3R8A).

tial biologically active compounds, namely, by introducing new pharmacophore centers in positions 2-, 3- and 4- of the 1,3-thiazole cycle, which was confirmed by the results of the virtual screening procedures performed.

Pharmacological screening for hypotensive activity was carried out *in vivo* in laboratory sexually mature nonlinear white rats of both sexes weighing 164,3 ± 3,1 g. During the experiment the animals were kept in the vivarium at the temperature 20–22 °C and relative humidity 40–60 %, under standard conditions on a balanced diet according to the current specifications, free access to food and water. The experiment was carried out in compliance with the requirements of the European Convention "On protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg, 1986). Before the study, the animals were quarantined and adapted to the laboratory room for 7 days.

Effect of the tested compounds on the cardiovascular system was determined by the parameters of blood pressure (BP) in the caudal arteries of the animal and the frequency of heart rate (HR) (Stefanov 2001). At first for all rats were simultaneously measuring these indicators using the sphygmomanometer (Ugo Basile, Italy) prior the introduction of test samples (output data). After registration output data rats divided into groups of 8 animals each (4 males and 4 females) randomly. Each compound was administered to rats of each individual group.

For screening studies of hypotensive activity doses of 7 mg/kg of body weight of the animal, intraperitoneally, were used. This dose is approximately 1/50 of the average lethal dose of the compound. The following registration of blood pressure and heart rate were carried out in 1 hour, 3 hours and 24 hours after intraperitoneal administration of each of the compounds.

The efficacy of the tested compounds was compared to the efficacy (antihypertensive effect) of the reference drug valsartan (Table 2). The results are presented in the arithmetic mean and the standard error of representativeness of the mean value (M ± m). Probability between the average values of the two samples was determined by Student's test for normal distribution differences between the control and experimental groups were considered to be statistically significant at $p < 0.05$.

Compound **3(2)** did not affect the functioning of the cardiovascular system in rats. After 3 hours after administration, there was a decrease of blood pressure by 14% for the administration of the compound **3(1)**. At the same time, in other terms of observation, this indicator has changed insignificantly. This compound had no effect on heart rate. The effect of compound **3(3)** was characterized by a decrease of this indicator by 11–12%, was quite stable regarding the influence on the blood pressure during the observation period. Significant hypotensive effect (a decrease of blood pressure by 16%) were observed for the administration of compound **3(4)** only within 3 hours after its administration, but later hypotensive effect was disappeared. After the administration of compound **3(6)** there was a decrease of blood pressure by 12% only 1 hour after its application, but in other observation periods, blood pressure remained at the level of output values. Gradually, blood pressure were decreased for the administration of compound **3(7)** at different observation periods – by 7%, by 9% and by 11% in 1 hour, 3 hours and 24 hours, respectively. The most significant effect on blood pressure among the tested compounds was the effect of compound **3(5)** – hydrobromide of 4-(4-bromophenyl)-N-[3-(trifluoromethyl)phenyl]-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine. This compound significantly lowered blood pressure in comparison with the output data in all terms of observation, and the hypotensive effect of this compound was characterized by a decrease of blood pressure by 18% after 3 hours and 24 hours after intraperitoneal administration, and was at the level of antihypertensive effect of the reference drug valsartan. It should be noted that significant changes in heart rate have not been registered. Reference drug Valsartan lowered blood pressure by 19.9%, 19.7% and 18.4% at 1 hour, 3 hours and 24 hours, respectively, and did not lead to a significant change in heart rate. Thus, the tested compounds, as well as the reference drug, did not affect the heart rate. Compounds investigated (except compounds **3(2)**) showed hypotensive effect different degrees of severity and duration.

A similar effect on the strength and duration of the hypotensive effect of reference drug valsartan was shown by compound **3(5)**, which suggests that the mechanism of action of this compound is due to the effect on angiotensin receptor II.

Table 2. Influence of intraperitoneally administered newly synthesized compounds on cardiovascular system in rats.

Compound	Output data		In 1 hour		In 3 hours		In 24 hours	
	BP	HR	BP	HR	BP	HR	BP	HR
3(1)	96.3 ± 2.6	366.7 ± 13.9	93.3 ± 2.9	374.4 ± 18.1	82.8 ± 2.6*	366.7 ± 16.1	89.2 ± 2.1*	370.4 ± 19.5
3(2)	93.2 ± 3.4	358.8 ± 16.1	93.3 ± 3.2	358.3 ± 15.1	92.9 ± 3.7	370.0 ± 13.9	89.2 ± 3.1	363.8 ± 13.9
3(3)	89.2 ± 3.2	368.3 ± 19.3	79.2 ± 2.4*	372.0 ± 12.2	78.5 ± 3.2*	370.8 ± 19.7	78.5 ± 2.2*	370.8 ± 19.9
3(4)	97.0 ± 1.9	378.3 ± 9.5	81.7 ± 3.8*	367.5 ± 11.2	84.9 ± 3.8*	373.3 ± 14.8	94.3 ± 2.8	367.9 ± 11.2
3(5)	93.5 ± 2.9	370.0 ± 11.2	84.2 ± 2.7*	365.8 ± 19.9	75.5 ± 3.2*	370.2 ± 12.8	75.5 ± 3.2*	374.0 ± 11.2
3(6)	94.5 ± 2.1	372.0 ± 17.2	83.3 ± 1.9*	366.7 ± 18.9	93.5 ± 2.8	367.0 ± 11.2	94.5 ± 2.4	370.0 ± 19.2
3(7)	89.2 ± 2.6	357.0 ± 19.6	82.2 ± 2.9	354.0 ± 12.5	81.2 ± 2.7	368.0 ± 12.6	79.4 ± 2.7	368.0 ± 13.9
Valsartan	88.8 ± 3.2	363.8 ± 11.5	71.1 ± 2.4*	374.5 ± 16.7	71.3 ± 3.6*	375.0 ± 12.5	72.5 ± 2.8*	368.9 ± 9.1

Notes: * – p<0,05 relative to output data; BP – blood pressure; HR – frequency of heart rate.

Conclusions

In order to expand the arsenal of biologically active substances of cardiotropic action a systematic series of new 4-aryl-N-(aryl)-3-(prop-2-en-1-yl)-2,3-dihydro-1,3-thiazol-2-imine derivatives were synthesized. The structure and purity of the compounds synthesized were confirmed by ^{1}H, ^{13}C NMR-spectroscopy and elemental analysis. Based on the results of docking studies using Autodock 4.2.6 software, selected compounds with the best affinity for protein biomes (PDB codes: 3R8A) are promising for experimental studies of hypotensive and cardiotropic activity. The most effective antihypertensive effect, which is similar in duration and strength of the effect of valsartan, was the effect of compound **3(5)**. A comparative analysis of the results of molecular docking and *in vivo* results suggests that there is a positive correlation between scoring protein inhibition and experimental data.

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