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Synthesis of 2-(4-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives and prediction of their biological activity

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ABSTRACT

The synthesis of new 2-(4-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives has been carried out. The structures and purity of synthesized compounds were verified on the basis of elemental analysis, ^1H NMR-spectroscopy and chromatography-mass spectrometry. To optimize the pharmacological screening of 2-(4-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives «drug-like» parameters have been calculated and simulation of biological properties has been done. It was established that 13 synthesized compounds comply with Lipinski's Rule of Five and can be recommended for experimental biological tests. Based on data PASS-prediction as priority directions for experimental trials screening for anti-ischemic and anti-inflammatory activity has been chosen. The most perspective substances for experimental biological tests were elected.

Keywords: 1,3-thiazole derivatives, synthesis, spectral characteristics, «drug-likeness», virtual screening.

INTRODUCTION

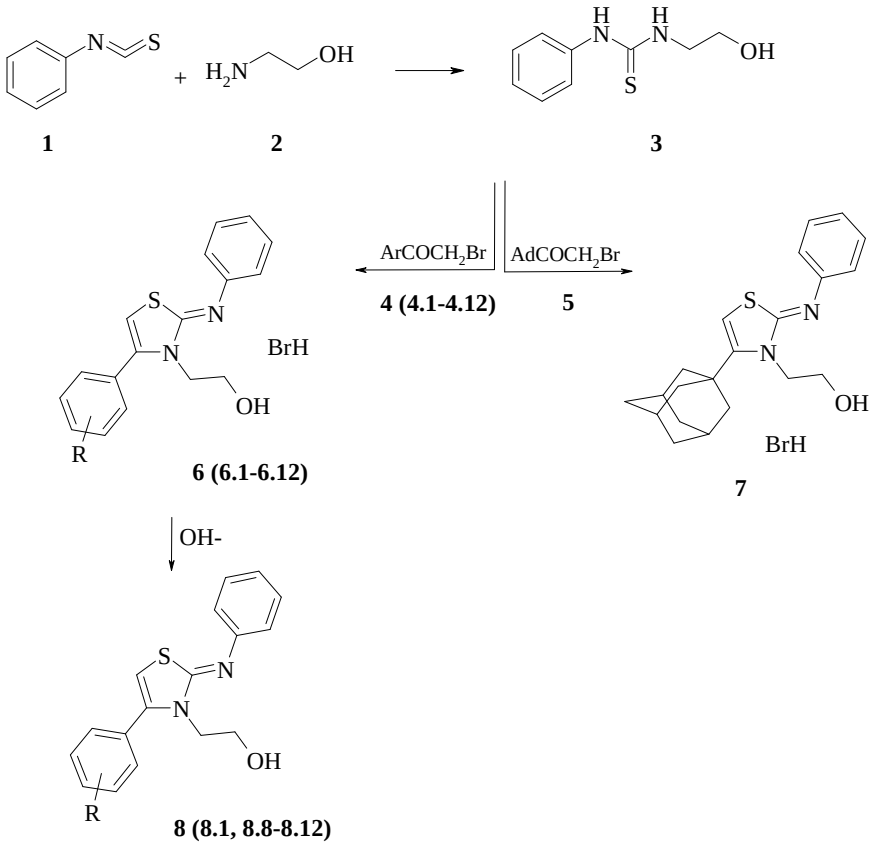
Nitrogen-containing heterocyclic systems occupy a privileged place among the heterocyclic compounds, because on the their base founded more than 2000 drugs. This fact convincingly shows the relevance and expediency of carrying out researches, aimed at developing new methodologies obtaining 5- and 6-membered nitrogen-containing heterocyclic systems with a powerful synthetic and biological potential [1].

Thiazol - 5-membered heterocyclic system with two heteroatoms: Sulfur and Nitrogen - is a part of highly efficient drugs as norsulfazol, phtalazol, miconazole, dithiazanine iodide and others. In addition, thiazole derivatives are the basis of thiamine (vitamin B_1), antibiotics penicillin and cephalosporin groups [2]. Among thiazole derivatives were founded substances with analgesic [3], spasmolytic [4], antioxidant and antiradical [5], antitumor [6] activities.

Based on the above, as the object of our study was elected 1,3-thiazole derivatives, namely 2-(4-R-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives. Purpouse of our work was the synthesis of new 2-(4-R-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives, confirmation of structure, calculation of «drug-like» parameters and simulation of biological properties synthesized compounds with further elimination of undesirable molecules to optimize the pharmacological screening.

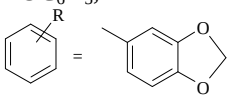
MATERIALS AND METHODS

Synthesis of 2-(4-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives ***6.1-6.7, 7, 8.1, 8.8-8.12*** has been carried out in several stages (Scheme 1):



Scheme 1

8.1 R= H,
8.2 R= 4-$CH(CH_3)_2$,
8.3 R= 4-OCH_3,
8.4 R= 4-OC_6H_5,



8.5 R=
8.6 R= 4-Cl,
8.7 R= 4-Br,
8.8 R= 4-CH_3,
8.9 R= 3-OCH_3,
8.10 R= 3,4-$(OCH_3)_2$,
8.11 R= 4-OC_2H_5,
8.12 R= 3-NO_2,

Intermediate N-(2-hydroxyethyl)-N'-phenylthiourea ***3*** was synthesized according to general method of obtaining unsymmetrical thioureas by interaction of phenylisothiocyanate ***1*** and 2-aminoethanol ***2*** [7]. Carrying out the reaction in the dry dioxane medium allows to raise the yield to 90%. Bromoketones ***4 (4.1-4.12), 5*** were obtained by bromination of corresponding acetophenones [8]. 2-(4-aryl-2-phenyliminothiazol-3-yl)-ethanol derivatives ***6.1-6.12*** were obtained by boiling for 1-3 hours equimolar amounts of N-(2-hydroxyethyl)-N'-phenylthiourea ***3*** and 2-bromo-1-aryl-ethanones ***4 (4.1-4.12)*** in the ethanol medium. 2-(4-Adamantan-1-yl-2-phenyliminothiazol-3-yl)-ethanol derivative ***7*** was obtained at similar conditions by the interaction of compound ***3*** and 2-bromo-1-adamantyl-ethanone ***5.*** Hydrobromic salts ***6.8-6.12*** were neutralized by 10% NH_4OH solution. The resulting precipitates were dried and crystallized. Target compounds ***6.1-6.7, 7, 8.1, 8.8-8.12*** were crystallized from organic solvents and obtained with the yields of 68-88%.

The target compounds – Hydrobromide 2-(4-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives ***6.1-6.7, 7*** - are white crystalline substances, soluble in water, insoluble in organic solvents.

The target compounds – 2-(4-aryl-2-phenyliminothiazol-3-yl)-ethanol derivatives ***8.1, 8.8-8.12*** - are white

crystalline substances, soluble in organic solvents, insoluble in water.

MATERIALS AND METHODS

Chemistry

All solvents were purified before use. Phenylisothiocyanate, 2-aminoethanol, acetophenone, 4-chloroacetophenone, 3,4-dimethoxyacetophenone, 1-adamantan-1-yl-ethanone and other acetophenones were purchased from Acros Organics and use without purification. Reactions were monitored by thin-layer chromatography (TLC) using Fluka silica gel (60 F 254) plates (0.25 mm). Visualization was made with UV light. Melting points of synthesized compounds were taken on a melting point tube. ^{1}H NMR spectra were recorded on Varian Gemini 400 MHz in DMSO-d6 using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm units use of d scale. The mass spectra were recorded on an Agilent LC/MSD SL 1100 instrument (USA). Elemental analysis of nitrogen content was carried out by Dumas method.

General procedure of the acetophenone bromination 4.1-4.12.

0,055 mol of bromine was added dropwise with such speed that the temperature of the reaction mixture did not exceed 35^{o}C to 0,05 mol of appropriate acetophenone in methanol (150 ml). After discoloration all of bromine reaction mixture was poured into 0,5 kg of crushed ice. Appropriate halohenketon was filtered, washed with water and dried.

General procedure of the synthesis of hydrobromide 2-(4-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives 6.1-6.7, 7.

Equimolar amounts of N-(2-hydroxyethyl)-N'-phenylthiourea ***3*** and 2-bromo-1-aryl(adamantyl)-ethanones ***4 (4.1-4.7), 5*** were boiled in ethanol for 1-3 hours while reaction monitoring by TLC. The obtained solid products ***6.1-6.7, 7*** were collected by filtration, washed with water and crystallized from the appropriate solvent.

General procedure of the synthesis of 2-(4-aryl-2-phenyliminothiazol-3-yl)-ethanol derivatives 8.1, 8.8-8.12.

Equimolar amounts of N-(2-hydroxyethyl)-N'-phenylthiourea ***3*** and 2-bromo-1-aryl-ethanones ***4 (4.8-4.12)*** were boiled in ethanol for 1-3 hours while reaction monitoring by TLC. The reaction mixture was poured off, boiled, evaporated till a volume of 15-20 ml and added 20 ml of 10% NH_4OH solution. The resulting precipitates were dried and crystallized.

Hydrobromide 2-(4-phenyl-2-phenyliminothiazol-3-yl)-ethanol 6.1.

Yield 82%, m.p.=197-98^{o}C (propanol-2). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3,63 (t, 2H, C$\underline{H}_2$CH$_2$OH), 4,21 (t, 2H, CH$_2$C$\underline{H}_2$OH), 7,02 (s,1H, CH-S). 7,41-7,62 (m, 10H, Ar-H). Anal. Calcd for $C_{17}H_{17}BrN_2OS$ N 7,42%. Found, %: N 7,44.

Hydrobromide 2-[4-(4^1-isopropylphenyl)-2-phenyliminothiazol-3-yl]-ethanol 6.2.

Yield 80%, m.p.=206-08^{o}C (ethanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1,24 (d, 6H, CH(C$\underline{H}_3$)$_2$), 2,99 (m, 1H, C$\underline{H}$(CH$_3$)$_2$), 3,65 (t, 2H, C$\underline{H}_2$CH$_2$OH), 4,20 (t, 2H, CH$_2$C$\underline{H}_2$OH), 6,99 (s,1H, CH-S), 7,42-7,61 (m, 9H, Ar-H). Anal. Calcd for $C_{20}H_{23}BrN_2OS$ N 6,68%. Found, %: N 6,69.

Hydrobromide 2-[4-(4^1-methoxyphenyl)-2-phenyliminothiazol-3-yl]-ethanol 6.3.

Yield 73%, m.p.=210-12^{o}C (propanol-2). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3,65 (t, 2H, C$\underline{H}_2$CH$_2$OH), 3,85 (s, 3H, OC$\underline{H}_3$), 4,26 (t, 2H, CH$_2$C$\underline{H}_2$OH), 6,90 (s,1H, CH-S), 7,05-7,43 (dd, 4H, Ar-H), 7,45-7,60 (m, 5H, Ar-H). Anal. Calcd for $C_{18}H_{19}BrN_2O_2S$ N 6,88%. Found, %: N 6,91.

Hydrobromide 2-[4-(4^1-phenoxyphenyl)-2-phenyliminothiazol-3-yl]-ethanol 6.4.

Yield 81%, m.p.=188-89^{o}C (methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3,65 (t, 2H, C$\underline{H}_2$CH$_2$OH), 4,21 (t, 2H, CH$_2$C$\underline{H}_2$OH), 6,95 (s,1H, CH-S), 7,00-7,72 (m, 14H, Ar-H). Anal. Calcd for $C_{23}H_{21}BrN_2O_2S$ N 5,97%. Found, %: N 6,03.

Hydrobromide 2-(4-benzo[1,3]dioxol-5-yl-2-phenyliminothiazol-3-yl)-ethanol 6.5.

Yield 71%, m.p.=217-19^{o}C (ethanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3,64 (t, 2H, C$\underline{H}_2$CH$_2$OH), 4,22 (t, 2H, CH$_2$C$\underline{H}_2$OH), 6,14 (s, 2H, O-CH$_2$-O), 7,06 (s,1H, CH-S), 6,99-7,63 (m, 8H, Ar-H). Anal. Calcd for $C_{18}H_{17}BrN_2O_3S$ N 6,65%. Found, %: N 6,65.

Hydrobromide 2-[4-(4^1-chlorophenyl)-2-phenyliminothiazol-3-yl]-ethanol 6.6.

Yield 85%, m.p.=223-25^{o}C (methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3,63 (t, 2H, C$\underline{H}_2$CH$_2$OH), 4,18 (t, 2H, CH$_2$C$\underline{H}_2$OH), 7,05 (s,1H, CH-S), 7,41-7,67 (m, 9H, Ar-H). Anal.Calcd for $C_{17}H_{16}BrClN_2OS$ N 6,80%. Found, %: N

6,82.

Hydrobromide 2-[4-(4[1]-bromophenyl)-2-phenyliminothiazol-3-yl]-ethanol 6.7.
Yield 80%, m.p.=221-22°C (methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3,63 (t, 2H, C<u>H</u>$_2$CH$_2$OH), 4,21 (t, 2H, CH$_2$C<u>H</u>$_2$OH), 7,05 (s,1H, CH-S), 7,43-7,78 (m, 9H, Ar-H). Anal. Calcd for $C_{17}H_{16}Br_2N_2OS$ N 6,14%. Found, %: N 6,16.

Hydrobromide 2-(4-adamantan-1-yl-2-phenyliminothiazol-3-yl]-ethanol 7.
Yield 85%, m.p. >290°C (methanol). Anal.Calcd for $C_{21}H_{27}BrN_2OS$ N 6,43%. Found, %: N 6,44.

2-(4-Phenyl-2-phenyliminothiazol-3-yl)-ethanol 8.1
Yield 81%, m.p.=84-85°C (hexane). Anal. Calcd for $C_{17}H_{16}N_2OS$, N 9,45%. Found, %: N 9,48. MS m/z: 297,2 [(M+H)+].

2-(4[1]-p-tolyl-2-phenyliminothiazol-3-yl)-ethanol 8.8
Yield 84%, m.p.=86-87°C (hexane). Anal. Calcd for $C_{18}H_{18}N_2OS$ N 9,02%. Found, %: N 9,06. MS m/z: 311,1 [(M+H)+].

2-[4-(3[1]-methoxyphenyl)-2-phenyliminothiazol-3-yl]-ethanol 8.9
Yield 79%, m.p.=103-104°C (hexane). Anal. Calcd for $C_{18}H_{18}N_2O_2S$ N 8,58%. Found, %: N 8,60. MS m/z: 327,5 [(M+H)+].

2-[4-(3[1],4[1]-dimethoxyphenyl)-2-phenyliminothiazol-3-yl]-ethanol 8.10
Yield 68%, m.p.=94-95°C (hexane). Anal. Calcd for $C_{19}H_{20}N_2O_3S$ N 7,86%. Found, %: N 7,92. MS m/z: 357,5 [(M+H)+].

2-[4-(4[1]-ethoxyphenyl)-2-phenyliminothiazol-3-yl]-ethanol 8.11
Yield 83%, m.p.=116-117°C (hexane). Anal. Calcd for $C_{19}H_{20}N_2O_2S$ N % 8,23. Found, %: N 8,26. MS m/z: 341,3 [(M+H)+].

2-[4-(3[1]-nitrophenyl)-2-phenyliminothiazol-3-yl]-ethanol 8.12
Yield 88%, m.p.=121-122°C (benzene). Anal.Calcd for $C_{17}H_{15}N_3O_3S$ N % 12,31. Found, %: N 12,35. MS m/z: 342,2 [(M+H)+].

The structures and purity of synthesized 2-(4-R-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives ***6.1-6.7, 7, 8.1, 8.8-8.12*** were confirmed by elemental analysis, ^{1}H NMR- and chromatography-mass spectra.

Development of effective medicinal substances is a lengthy process and requires a huge financial cost. Therefore more often initial phase of search pharmacologically active substances is application of methods *in silico*, in particular virtual screening [9].

Application a computer program PASS-online and «drug-like» parameters are the effective methods of virtual screening in searching of potential candidates for the drug substance and predicting of biological activity [10].

Physical and chemical properties of drug`s molecules play an important role in pharmacokinetic processes. A number of average values of physical and chemical parameters that determine the bioavailability, have been calculated for tested substances ***6.1-6.7, 7, 8.1, 8.8-8.12*** by using computer programs ACD/Labs and Molinspiration. These values have been compared with optimal and maximum allowable values according to «The rule of 5» Lipinski [11]. Molecular weight, molar refraction, number of hydrogen bond donors and acceptors have been calculated by using program Molinspiration, and partition-coefficient - by using ACD/Labs.

Any chemical substance can not be practically investigate on all known types of physiological activity [12]. Therefore, in order to optimize experimental pharmacological researches prediction of biological activity of the synthesized compounds ***6.1-6.7, 7, 8.1, 8.8-8.12*** has been performed in the online version of the computer program PASS (Prediction of Activity Spectra for Substances) [13]. The basis of this program is universal mathematical algorithm of establishment of dependency between the structure and biological properties with an average accuracy of prediction over 95% [14].

RESULTS AND DISCUSSION

Theoretically cyclization of unsymmetrical thioureas is possible in two ways - benzene ring of thiourea residue in thiazole can be both at the exocyclic Nitrogen atom, and at the endocyclic Nitrogen atom. Our assumptions regarding the location of the benzene ring for the synthesized compounds ***6.1-6.7, 7, 8.1, 8.8-8.12*** at the exocyclic Nitrogen atom is based on the basis of literature data concerning the passage of cyclization for similar structures [15-18].

Chromatographic purity and molecular ion peak registration for the 2-(4-R-aryl-2-phenyliminothiazol-3-yl)-ethanol derivatives ***8.8-8.12*** has been established using chromatography-mass spectra.

Analysis of ^{1}H NMR spectra of the 2-(4-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives ***6.1-6.7*** are displayed well defined general resonance signals of the aromatic protons as multiplets at δ=7,00-7,80 ppm and of the methine proton of thiazole cycle as singlet at δ=6,90-7,05 ppm. The signals of ethanol residue protons for all compounds are presented at spectra as triplets at δ=3,63-3,65 ppm (methylene group is not connected with an Oxygen atom) and at δ=4,18-4,26 ppm (methylene group connected with Oxygen atom).

Analysis of the results of calculation drug-like parameters (Table 1) showed that tested compounds, except hydrobromide 2-[4-(4^1-phenoxyphenyl)-2-phenyliminothiazol-3-yl]-ethanol ***6.4***, have average values of drug-like parameters, which are close to optimum values. It means that 13 tested compounds have no deviations from the rules Lipinski and it can provide good bioavailability at oral administration. The data in Table 1 is an important argument for further experimental pharmacological screening of synthesized compounds.

Table 1 The value of «drug-like» parameters of 2-(4-R-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives

Compound	Descriptor				
	MW [1]	MR [2](см^3)	Log P [3]	nOHNH[4]	nON[5]
6.1	377,3	88,91	4,02	1	3
6.2	419,38	102,37	5,36	1	3
6.3	407,42	94,73	4,00	1	4
6.4	469,39	115,41	6,01	1	4
6.5	421,31	93,45	4,06	1	5
6.6	411,74	93,51	4,74	1	3
6.7	456,19	96,47	4,91	1	3
7	435,42	102,78	5,24	1	3
8.1	296,39	88,91	4,02	1	3
8.8	310,41	93,34	4,48	1	3
8.9	326,41	94,73	3,97	1	4
8.10	340,44	99,34	4,50	1	4
8.11	356,44	100,54	3,85	1	5
8.12	341,38	94,57	4,38	1	6
Interval of values	296,39-469,39	87,51-115,41	3,84-6,01	1	3-6
Average value	413,05	96,43	4,49	1	3,73
Maximum permissible value	460	130	5,6	5	10
Optimal value	357	97	2,52	≤ 5	≤10

1 - molecular weight; 2 - molar refraction; 3 - partition-coefficient; 4 - number of hydrogen bond donors; 5 - number of hydrogen bond acceptors.

*To choose priority directions for experimental screening of biological activity of 2-(4-R-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives **6.1-6.7, 7, 8.1, 8.8-8.12** the results of PASS-online prediction have been analyzed (Table 2).*

Based on data PASS-prediction, all synthesized compounds with an index of activity Pa 0,77-0,85 can possess properties anaphylatoxin receptor antagonists. It should be noted that the highest activity index (0,85) have substances with phenyl and p-chlorophenyl radical (compounds ***6.1, 8.1*** and ***6.6***, respectively). According to the results of computer prediction in the spectrum of pharmacological activity of the synthesized compounds is a high probability of manifestation of antiischemic and cerebral (Pa=0,43-0,67), anti-inflammatory (Pa=0,44-0,63) and antidiabetic (Pa=0,38-0,59) activity. Theoretically there is a possibility to use the compounds of this group for the treatment of atherosclerosis (Pa=0,46-0,61) and allergic rhinitis (Pa=0,36-0,51), and also ability to be K(ir) 6.2 channel activators (Pa=0,50-0,62). As the results suggest all compounds except for 2-(4-benzo[1,3]dioxol-5-yl-2-phenyliminothiazol-3-yl)-ethanol ***6.5*** have antipruritic activity with Pa from 0,34 to 0,60.

Table 2 Indexes of biological activity of 2-(4-R-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives calculated by the program PASS-online

Compound	Activity, Pa/Pi							
	Anaphylatoxin receptor antagonist	K(ir) 6.2 channel activator	Antiischemic, cerebral	Anti-inflammatory	Atherosclerosis treatment	Antidiabetic	Antipruritic	Allergic rhinitis treatment
6.1	0,85 0,01	0,62 0,00	0,56 0,08	0,58 0,04	0,6 0,01	0,59 0,01	0,52 0,03	0,51 0,00
6.2	0,77 0,02	0,56 0,00	0,43 0,16	0,63 0,03	0,61 0,01	0,54 0,02	0,59 0,02	0,4 0,01
6.3	0,77 0,02	0,56 0,00	0,47 0,13	0,55 0,04	0,53 0,02	0,51 0,02	0,5 0,04	0,43 0,01
6.4	0,82 0,01	0,58 0,00	0,59 0,06	0,55 0,04	0,59 0,01	0,58 0,01	0,48 0,04	0,47 0,00
6.5	0,77 0,02	0,55 0,00	0,67 0,04	0,44 0,08	0,5 0,02	0,38 0,05	-	0,38 0,01
6.6	0,85 0,01	0,59 0,00	0,59 0,06	0,55 0,04	0,57 0,01	0,56 0,02	0,48 0,04	0,47 0,00
6.7	0,79 0,01	0,58 0,00	0,43 0,16	0,44 0,08	0,52 0,02	0,54 0,02	0,34 0,08	0,46 0,00
7	0,79 0,01	0,50 0,00	0,58 0,07	0,47 0,07	0,48 0,02	0,56 0,02	0,60 0,02	0,36 0,01
8.1	0,85 0,01	0,62 0,00	0,56 0,08	0,58 0,04	0,6 0,01	0,59 0,01	0,52 0,03	0,51 0,00
8.8	0,80 0,01	0,58 0,00	0,53 0,09	0,57 0,04	0,57 0,01	0,55 0,02	0,52 0,03	0,47 0,00
8.9	0,78 0,01	0,57 0,00	0,48 0,12	0,54 0,05	0,54 0,01	0,52 0,02	0,48 0,04	0,44 0,00
8.10	0,79 0,01	0,56 0,00	0,54 0,08	0,53 0,05	0,56 0,01	0,58 0,01	0,47 0,04	0,43 0,01
8.11	0,77 0,02	0,56 0,00	0,44 0,15	0,55 0,04	0,51 0,02	0,47 0,03	0,5 0,04	0,44 0,00
8.12	0,79 0,01	0,59 0,00	0,54 0,09	0,47 0,07	0,46 0,03	0,42 0,04	0,41 0,06	0,43 0,01

CONCLUSION

1. The synthesis of undescribed in the literature 2-(4-R-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives was carried out for the purpose of searching for new biologically active compounds and the structure of synthesized compounds were confirmed by elemental analysis, ^{1}H NMR- and chromatomass-spectra.

2. All compounds were tested for compliance Lipinski's Rule of Five; by test results, twenteen 2-(4-R-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives comply with requirements and can be recommended for experimental biological tests.

3. Screening for anti-ischemic and anti-inflammatory activity as priority directions for experimental trials was chosen. The most perspective substances for experimental biological tests were elected.

REFERENCES

[1] M Vovk, *Visn. NAS of Ukraine*, **2015**, 3, 38–43.
[2] M Mashkovskiy; *Drugs: in 2 volumes, Moskow, New wave, 14 edition*, **2002**, 608.
[3] S Demchenko, O Yadlovsky, L Bobkova, T Buhtiarova, *Pharm. Journal*, **2012**, 3, 49-54.
[4] Y Kononevych, A Demchenko, *Journal of org. and pharm. chemistry*, **2011**, 9, 1, 52-56.
[5] S Demchenko, O Smolsky, L Bobkova, *Pharmacology and medical toxicology*, **2012**, 6, 47-51.
[6] S Demchenko, L Bobkova, *Pharm. Journal*, **2012**, 1, 34-41.
[7] A Lourenço, M Saito, L Dorneles, G Viana, P Sathler, L Aguiar et al, *Molecules*, **2015**, 20, 7174–7200.
[8] K Chidan; K Chong; M SiauHui; C TzeShyang; L Wan-Sin; Q ChingKheng et al, *Molecules*, **2015**, 20, 10; 18827 – 18846.
[9] N Pshenkyna, *Bio-medical journal*, **2011**, 12, 1048–1066.
[10] N Monka, S Vasylyuk, G Shiyan, V Lubenets, *Collection of centre of scientific publications Part 2: «Science Achievements in 2014»: collection of articles*, **2014**, 111–114.
[11] C Lipinski, F Lombardo, B Dominy, P Feeney, *Advanced Drug Delivery Reviews*, **2012**, 64, 4–17.
[12] A Lagunin, DFilimonov, V Poroikov, *Chem-pharm. Journal.*, **2001**, 35, 7, 28-34.
[13] PASS online [Electronic resource] – http://www.pharmaexpert.ru/passonline/.

[14] D Filimonov, A Lagunin, T Gloriozova, A Rudik, D Druzhilovsky, P Pogodin, V Poroikov, *Chemistry of heterocyclic compounds*, **2014**, 3, 483—499.
[15] *Patent*; GLAXO GROUP LIMITED; A1 WO2007/122241; **2007**.
[16] *Patent*; GLAXO GROUP LIMITED; A1 WO2009/53448; **2009**.
[17] *Patent*; Ulrich, Peter C.; Cerami, Anthony; A1 US2003/186993; **2003**.
[18] H Tripathy et al.; *Indian Journal of Chemistry*, ***1971***, 9, 1232 - 1235.