SYNTHESIS, DOCKING STUDIES OF THE DERIVATIVES OF 3-ALLYL-N,4-DIPHENYL-THIAZOLE-2-IMINE

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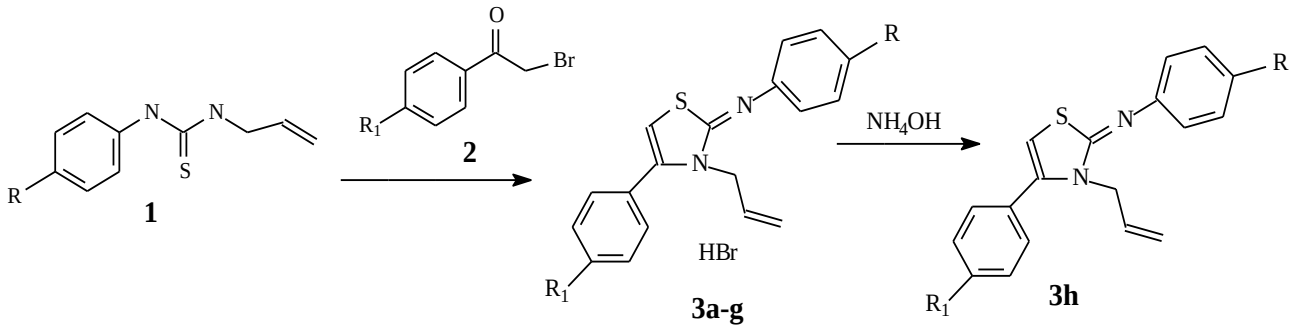
Introduction. Thiazoles, due to the presence of substituents capable of being modified, represent scientific value in organic synthesis for the production of new biologically active substances and therefore have a perspective to be used in medicine and pharmacy.

Aim. The purpose of this study is to synthesize new biologically active compounds in the series of the derivatives of 3-allyl-N,4-diphenyl-thiazole-2-imine, confirm the structure of synthesized compounds, conduct in silico probable molecular mechanisms of cardioprotective action of the obtained substances by the method of flexible molecular docking.

Materials and methods. The starting, auxiliary substances and solvents used in the work were obtained and purified using standard techniques. The purity of the obtained compounds was monitored by thin layer chromatography method using silica gel of Fluka (60 F254) plate (0.25 mm). Visualization was carried out by UV-radiation. Elemental analysis of the nitrogen content was carried out by the Dumas method. ^{1}H NMR-spectra were registered on a Varian Gemini 400 MHz device in DMSO-d6, tetramethylsilane (TMS) was used as an internal standard. For flexible molecular docking, the Autodock 4.2.6 software package was used. Preparation of ligands was carried out with the help of programs Vega ZZ (command line) and MGL Tools 1.5.6. The active center of the macromolecule from Protein Data Bank (PDB) of the gamma-butyrobetaine hydroxylase enzyme (PDB ID: 3O2G) was used as a biological target. Visual analysis of the complexes of the substances in the active center of the enzyme was carried out using the program Discovery Studio Visualizer 4.0.

Results and discussion. Under the conditions of the Hantzsch reaction, the synthesis of the derivatives of 3-allyl-N,4-diphenyl-thiazole-2-imine ***(3a-g)*** hydrobromide was carried out due to the interaction of the derivatives of unsymmetrical thioureas ***1*** with α-bromo-4-R-acetophenone ***2*** in equimolar amounts by boiling in ethanol for 3 hours, 3-allyl-N,4-diphenyl-thiazole-2-imine ***3h*** was obtained by neutralizing the corresponding hydrobromide with a 10% solution of NH_4OH:



where: ***3a*** R=CH_3, R_1 =OCH_3; ***3b*** R=CH_3, R_1 =Cl; ***3c*** R=CH_3, R_1 =2',4'-$(Cl)_2$; ***3d*** R=Br, R_1 =Cl; ***3e*** R=H, R_1 =Cl; ***3f*** R=Br, R_1 =NO_2; ***3g*** R=CH_3, R_1 =CH_3; ***3h*** R=CH_3, R_1 =OCH_3

The structure of the obtained compounds is confirmed by modern physicochemical methods of analysis: ^{1}H-NMR, 2DNMR-spectroscopy (NOESY, ROESY), elemental analysis, thin-layer chromatography. The conducted studies prove the regioselectivity of the reaction to the formation of substituted 3-allyl-N,4-diphenyl-thiazole-2-imines.

The conducted docking studies have shown that the pharmacological action of the synthesized compounds, as potential cardioprotective agents of metabolic action, is connected with inhibition of gamma-butyrobetaine hydroxylase (PDBID: 3O2G). Values of scoring functions for all investigated substances are negative and in absolute values are comparable or exceed values of scoring functions for standard substances, that indicates a high thermodynamic probability of the display of inhibitory activity in relation to this enzyme. The obtained results indicate the possibility of the formation of stable complexes of substituted thiazole-2-imines with a biological target in which the arrangement of the ligands in the active center of the receptor and the amino acids residues of the side chains, involved in the formation of non-covalent bonds, are analogous to the geometry and types of binding of levocarnitine and mildronate, established on the basis of crystallographic studies.

The derivatives of thiazole-2-imine can be considered as a promising scaffold for the formation of combinatorial libraries of potential biologically active substances, namely by introducing new pharmacophore centers into the 3 position of the thiazole cycle, as proved by the results of the conducted virtual screening procedures.

Conclusions. The synthesis of 8 new biologically active compounds of the derivatives of 3-allyl-N,4-diphenyl-thiazole-2-imine under the conditions of the Hantzsch reaction was carried out. The structure of the synthesized compounds is confirmed by the integrated use of modern physicochemical methods of analysis. The results of the docking studies allow to state that the new derivatives of 3-allyl-N,4-diphenyl-thiazole-2-imine are potential cardioprotective agents of metabolic action.