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Study of the effect of the structure of pioglitazone derivatives on the main parameters of binding to the endothelial growth factor of blood vessels VEGF-A in silico

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Pioglitazone is a drug of the thiazolidinedione class that is used as a hypoglycemic agent in type 2 diabetes. The very effect of this drug is manifested in its ability to reduce insulin resistance. Recently, there is more and more information in the literature about new functionalized derivatives of pioglitazone that exhibit a wide range of antitumor activity with different molecular mechanisms of action [1]. It is also known that fast-growing tumor cells produce protein molecules that stimulate the germination of blood capillaries that provide its nutrition. These molecules are called growth factors. The main one is vascular endothelial growth factor (VREF), better known by the English name "vascular endothelial growth factor" (VEGF). The VEGF family of molecules includes several factors: VEGF-A, -B, -C, -D, -E, and placental growth factor PlGF. VEGF-A, -B and PlGF are the main regulators of blood vessel growth, VEGF -C and-D are essential for the formation of lymphatic vessels. VEGF-A is one of the most well-studied factors of angiogenesis, which is considered as a point of application of a number of new drugs for the treatment of cancer and retinal diseases [2]. Many of them were included in the first and second lines of treatment for renal cell carcinoma, breast cancer and other localizations, as well as age-related and vascular lesions of the retina. In this paper, we studied the effect of the introduction of new functional groups into the structure of pioglitazone on the main parameters of the binding of pioglitazone derivatives to the endothelial growth factor of blood vessels (VEGF-A).

Objective. To identify the functionalized pioglitazone derivative with the lowest free binding energy, the lowest inhibition constant, and the largest binding area to VEGF-A.

Materials and methods. The design of pioglitazone derived structures (13 samples) was performed using specialized chemical programs ChemOffice. The selection of receptor proteins was carried out from the 3D protein structure and nucleic acid data Bank (PDB). Molecular docking in silico is performed using the Dockingserver program.

The results of the study. In the *in silico* study, the relationship between structure (structure and stereochemistry) and biological activity was established. It is shown that the nature of the functional groups and the relative configuration of the stereoisomers affect the binding energy of the studied compounds to VEGF-A. In the course of molecular docking and analysis of

the obtained data, it was determined that the best indicators of the free binding energy, the inhibition constant, and the binding area were found in a sample with an S-configuration of the chiral center, containing two chlorine atoms in the benzene cycle, an m-bromophenyl radical, and morpholine in the thiadol cycle (-5.92 Kcal/mol; Ki = 45.99 uM: S = 663.829).

Conclusions. As a result of the study, pioglitazone derivatives with strong binding to VEGF-A were identified, and the structure-biological activity relationship was established. The results of the study can later be used for the synthesis of pioglitazone derivatives when studying them as VEGF-A inhibitors.

References

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