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IN SILICO RESEARCH OF THE MOLECULAR MECHANISMS OF THE ANTI-INFLAMMATORY AND ANALGESIC ACTION OF 3-(CARBOMOYL-PROPIONYLAMINO)-2-PHENYLAMINOBENZOIC ACID DERIVATIVES

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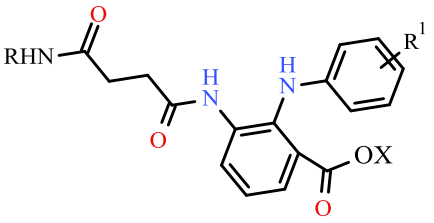
An important direction in the development of modern medical chemistry is the use of computer simulations in the process of finding new drugs. Molecular docking, in which the parameters of binding of ligands to receptors is evaluated, is now preceded by pharmacological studies [1-3] . The use of this methodology allows to optimize the structures of "leader compounds"; to conduct a virtual screening to determine the affinity of compounds to a particular biological target; to model binding of the target ligand, taking into account the specificity of the interactions.

The purpose of the study is research of probable mechanisms of anti-inflammatory and analgesic action of 3-(carbomoyl-propionylamino)-2-phenylaminobenzoic acid derivatives on the cell and subcellular levels using the molecular docking method.

For the docking studies, crystallographic structural models with a high separation capacity with Protein Data Bank were used: COX-1 in complex with α-methyl-4-diphenylacetic acid (pdb code 1Q4G), COX-2, crystallized with naproxene (pdb code 3NT1) and mPGES-1 in complex with glutathione (pdb code 4AL0) [4-6]. The flexible molecular docking was conducted using software package Molecular Operating Environment (MOE) [7]. Docking studies were conducted for 16

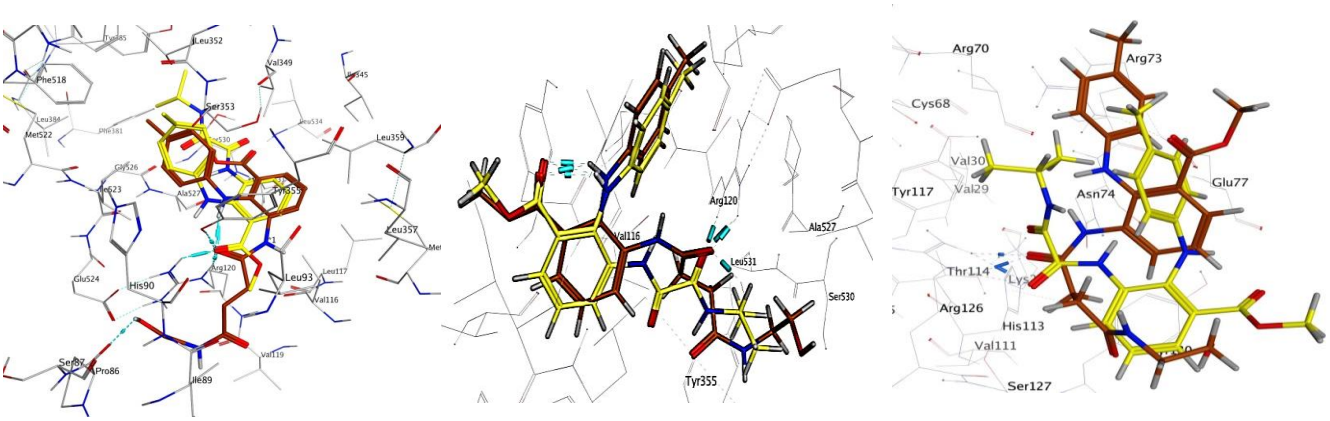
substances of derivatives of 3- (carbomoyl-propionylamino)-2-phenylaminobenzoic acid the chemical structure:



X = H, CH_3
R = CH_3, $(CH_2)_2OH$
R^1 = 2-CH_3 , 4-CH_3 , 3,4-$(CH_3)_2$, 4-OC_2H_5, Cl

According to the results of the docking studies four scoring functions were calculated (Affinity dG Scoring, Alpha HB Scoring, London dG Scoring, GBVI/WSA dG Scoring). The scoring functions for all substances under study have negative values and are comparable or exceed values of the scoring functions of voltaren, analgin, and naproxen. The values obtained indicate a thermodynamic probability and the energy capacity of the formation of complexes between the molecules of the investigated substances and the corresponding receptor, in which the arrangement of the ligands in the active center of the receptor and the amino acids residues of the side chains are similar to the geometry and binding types of the known inhibitors of COX-1, COX-2 and microsomal prostaglandin-E-synthase-1 (mPGES-1), established on the basis of crystallographic studies.

The visualization of the results of molecular docking is shown in Fig. 1.



a b c

Fig. 1. Superpositions of the molecules under study in active centers COX-1(a), COX-2 (b) and mPGES-1 (c)

Thus, the results of a flexible molecular docking of derivatives of 3-(carbomoyl-propionylamino)-2-phenylaminobenzoic acids to COX-1, COX-2 and mPGES-1 indicate the possibility of forming stable complexes between them, in which for all compounds studied binding between the ligand and the receptor occurs with participation of Oxygen atoms of the carboxyl group of 2-aminobenzoic acid or Oxygen carbonyl atoms in the residues of dicarboxylic acids in the form of hydrogen, as well as π-H or π-π interactions involving the phenyl ring of 2-(phenyl)aminobenzoic acid.

The results of molecular docking have shown that the possible mechanism of anti-inflammatory activity of derivatives of 3-(carbomoyl-propionylamino)-2-phenylaminobenzoic acids involves COX-2 inhibition. The conducted studies have revealed the leader compounds, which can be used in subsequent pharmacological studies on anti-inflammatory and analgesic activity.

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