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DOCKING STUDIES AND ANTI-INFLAMMATORY ACTIVITY OF A PROSPECTIVE SUBSTANCE 3-MONOETHANOLAMINE SUCCINOYLAMIDO-N-(3',4'-DIMETHYLPHENYL)ANTHRANILIC ACID

ROHALSKA K.O.,
SULEIMAN M.M.,
YAREMENKO V.D.,
KOBZAR N.P.,
ALFEROVA D.O.
Department of Medicinal Chemistry
The National University of Pharmacy
Kharkiv, Ukraine

The search for biologically active compounds of direct pharmacological effect, development and perfection of theoretical (*in silico*) research methods of mechanisms of medicinal agents' action, foresight of their activity, virtual design of new medicine-like substances are important courses of modern pharmaceutical chemistry development.

The purpose of current work is the research on anti-inflammatory activity of a prospective substance 3-monoethanolamine succinoylamido-N-(3',4'-dimethylphenyl) anthranilic acid and determination of its probable mechanism of action using flexible molecular docking.

Anti-inflammatory activity was studied on the model of carrageenan swelling on sub-plantar injection of 0,1 ml of carrageenan solution in mice. The studied substance and reference medicine (sodium diclofenac) were injected intragastrically in the dose of 10, 20 mg/kg 1 hour prior to the phlogogen injection. Animals of control group were given distilled water. Anti-inflammatory activity of 3-monoethanolamine succinoylamido-N-(3',4'-dimethylphenyl) anthranilic acid was almost twice as high as in sodium diclofenac. High activity is associated with the presence of two methyl radicals in the 3rd and 4th positions of the non-anthranilic

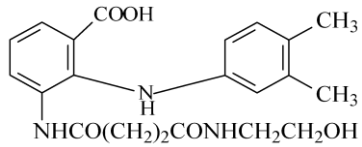
fragment of the molecule, as well as with the presence of a hydroxyethyl substituting group in the succinic acid fragment [1].

Crystallographic structural models from Protein Data Bank with high resolution were used in docking research: COX-1 in complex with у комплексі з α-methyl-4-diphenylacetic acid (pdb code 1Q4G) [2], COX-2, co-crystallized with naproxen (pdb code 3NT1) [3] and mPGES-1 in complex with glutathione (pdb code 4AL0) [4]. Flexible molecular docking was carried out using Molecular Operating Environment (MOE) software [5]. Energy minimizing of all obtained conformers was carried out using force field MMFF94x and stopped when the root mean square gradient (RMS gradient) reached the value lower than 0,01, at set number of performed iterations not higher than 200. Conformers, the energy value of which exceeded the minimal calculated energy value for the substance more than by 7 ccal/mol, were excluded from the database as energetically unfavourable ones. In addition to the above, maximum quantity of generated conformers for each of the compounds was set at the level of 200. Preliminary optimization of the receptors' structure included calculation of partial charges on atoms and the 3*D* protonation procedure at pH=7,4, aimed at determination and correction of ionization state of acidic and alkaline functional groups as parts of the residues of certain amino acids, as well as the position of hydrogen atoms in the structure of a peptide macromolecule. 3*D* protonation function allows automatically optimizing the orientation of hydrogen atoms in the way to increase the possibility of their hydrogen bond formation along with general energy minimizing. Then the final gradient energy minimization actuated by force field AMBER99 was carried out until the RMS gradient reached the 0,01 value. "Dummy atoms" were created in the receptor's active center and the residues of amino acids (alpha centers) within a 4,5 Å radius were chosen. Assessment of possible ligand positions in the receptor's active center was carried out using iteration procedure, in which a randomly chosen conformer was placed in the binding site in a way for the superposition of three random ligand's atoms and three receptor's active centers to happen.

The values of calculated scoring functions for complexes formed by the 3-monoethanolamine succinoylamido-N-(3',4'-dimethylphenyl) anthranilic acid molecule with COX-1, COX-2 and mPGES-1 are given in Table 1.

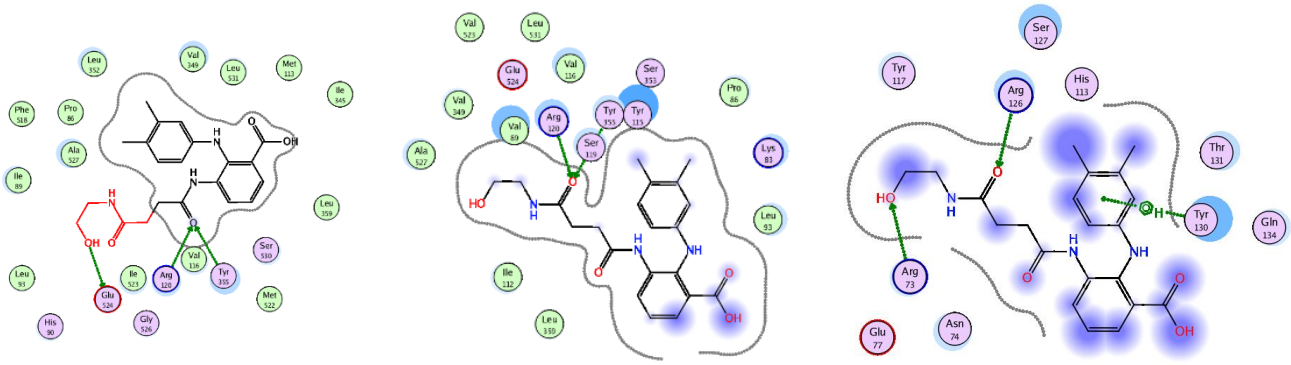
Table 1

Results of flexible molecular docking of the studied compound to COX-1, COX-2 and mPGES-1

	Biotargets	Scoring functions			
		GBVI/WSA dG	London dG	Alpha HB	Affinity dG
	COX-1	6,2469	-8,4174	-134,6355	-4,5163
	COX-2	-6,4466	-9,4861	-119,2825	-5,6401
	mPGES-1	-4,1109	-3,3687	-53,6302	-2,3066

Thus, it may be assumed that the inhibitory activity of the studied compound towards COX-1, COX-2 and mPGES-1 may be implemented by forming complexes between them, the stability of which is provided mainly due to energetically advantageous geometrical ligand position in this receptor's active center, formation of hydrogen bonds between them, thermodynamical probability of such binding is confirmed by negative values of scoring functions.

The studied substance is able to bind to COX-1 by forming one or two hydrogen bonds between the carbonyl oxygen atom of carbamoyl and Arg120 and Tyr355. Hydrogen bond is also formed between the hydroxyethyl fragment oxygen atom and Glu524. In case of complex formation with COX-2 hydrogen bonds appear between the carbonyl oxygen atom of carbamoyl and Arg120 and Tyr355. As for the complexes with mPGES-1, hydrogen bonds are formed between the hydroxyethyl fragment oxygen atom and Arg73, and the carbonyl oxygen atom of carbamoyl – with Arg126. Additional stabilizing of the complex appears due to the π-H interaction between the aromatic ring of anthranilic acid and Tyr130 (Fig. 1).



a) b) c)

Fig. 1. Diagrams of ligand interactions in complexes with COX-1 a), COX-2 b) and mPGES-1 c)

The results of molecular docking have shown that the possible mechanism of anti-inflammatory activity of a prospective substance 3-monoethanolamine succinoylamido-N-(3',4'-dimethylphenyl) anthranilic acid involves COX-2 inhibition.

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