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Docking Studies of the Derivatives of 3-oxamoyl(succinoyl)amides of N-Phenylanthranilic Acids as Inhibitors of Enzymes COX-1 and COX-2

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ABSTRACT

Conducted docking studies found that pharmacological activity is associated with inhibiting prostaglandin synthesis by new derivatives of N-phenylanthranilic acid by inhibiting enzyme activity by them, involved in different stages of cyclooxygenase pathway of metabolism of arachidonic acid: COX-1, COX-2. The obtained results indicate the possibility of the formation of stable complexes of the molecules of the synthesized substances with COX-1 and COX-2, in which the location of the ligands in the active center of the receptor and the residues of amino acids of side chains, involved in the formation of non-covalent bonds, are analogical to the geometry and types of binding of classical nonsteroidal anti-inflammatory drugs, established basing on crystallographic researches.

Keywords: 3-oxamoyl(*succinoyl*)*amides*, N-phenylanthranilic acids, Anti-inflammatory activity, Analgesic activity, Docking studies

INTRODUCTION

An important focus of the development of modern medicinal chemistry is the study of the mechanisms of action of the newly synthesized compounds on cellular and subcellular levels using a methodology of assessing the binding of ligands with likely biological targets.

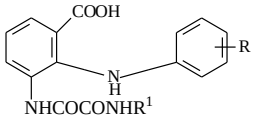
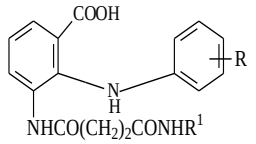
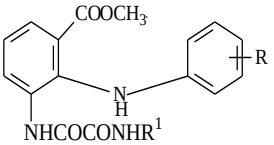
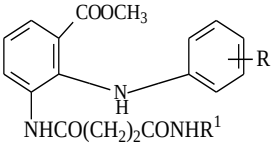
According to the results of pharmacological screening and QSAR-analysis of the derivatives of 3-oxamoyl(*succinoyl*)*amides* of N-phenylanthranilic acids it was found that they have a moderate and high anti-inflammatory, analgesic activity compared to the reference-drugs such as sodium diclofenac and sodium metamizole (Table 1) [1].

Arachidonic acid, formed during the release of phospholipids from cell membranes, can be metabolized by cyclooxygenase or lipoxygenase way. Cyclooxygenase way in the stage of transformations of arachidonic acid leads to the formation of prostaglandin H2 (PGH2), which takes place in two stages: oxidation of arachidonic acid to prostaglandin G2 (PGG2) with its subsequent restoration to PGH2 that is a precursor in the biosynthesis of other types of prostaglandins (PGD2, PGE2, PGF2, PGI2), thromboxane A2 and prostacyclin [2]. Biosynthesis of PGH_2 is provided by the enzymatic activity of two isoforms of cyclooxygenase –COX-1 and COX-2 [3,4]. COX-1 is a constitutive form of the enzyme contained in almost all tissues and cells of the body and regulates the processes of the synthesis of homeostatic and cytoprotective prostaglandins in the mucosa of the gastrointestinal tract, endothelium, platelets and the kidney. The production of COX-2 formation in many tissues is induced only under the influence of pathologic incentives, particularly in the occurrence of inflammatory reaction. The inhibition of the prostaglandin synthesis is associated with the inhibition of the activity of cyclooxygenase enzyme. In this connection, it can be predicted that the mechanism of anti-inflammatory action of new compounds will be similar to the action of many classic nonsteroidal anti-inflammatory drugs (*NSAIDs*), connected with inhibitory effects on those enzymes.

MATERIALS AND METHODS

For docking studies, crystallographic structural models with high resolution capability with the Protein Data Bank were used: COX-1 in complex with α-methyl-4- diphenylacetic acid (pdb code 1Q4G) [5], COX-2, cocrystallized with naproxen (pdb code 3NT1) [6]. A flexible molecular docking was conducted using the software package Molecular Operating Environment (MOE) [7]. Before the start of conducting the procedure of docking, the base of conformers was created for 33 synthesized compounds- *3-oxamoylsubstituted and 3-succinoylsubstituted* N-phenylanthranilic acids and their methyl esters, due to a systematic conformational search using Moe.

Table 1: Anti-inflammatory and analgetic activity of 3-oxamoyl(*succinoyl*)*substituted* N-phenylanthranilic acids and their methyl esters

Compound	Formula	R	R^1	Anti-inflammatory		Analgetic	
				Dose, mg/kg	Activity, %	Dose, mg/kg	Activity, %
1	2	3	4	5	6	7	8
1		H	H	20	17,7	20	20,4
2		2'-CH_3	CH_3	20	29,5	20	40,3
3		3'-CH_3	$(CH_2)_2OH$	20	39,5	20	49,4
4		4'-CH_3	C_3H_7-i	20	40,6	20	50,1
5		3',4'-$(CH_3)_2$	C_4H_9-н	20	0	20	0
6		4'-CH_3	CH_3	20	27,5	20	19,2
7		4'-OC_2H_5	CH_3	20	30,8	20	24,5
8		2'-Cl	CH_3	20	32,7	20	35,2
9		4'-Cl	CH_3	20	27,8	20	30,7
10		2'-CH_3	CH_3	10 20	9,1 25,1	10 20	0 184
11		2'-CH_3	$(CH_2)_2OH$	10 20	0 15,1	10 20	0 25,4
12		4'-CH_3	CH_3	10 20	0 17,3	10 20	0 0
13		4'-CH_3	$(CH_2)_2OH$	10 20	20,4 33,5	10 20	31,4 39,4
14		3',4'-$(CH_3)_2$	CH_3	5,4	62,5	6,3	61,2
15		3',4'-$(CH_3)_2$	$(CH_2)_2OH$	5,3	65,3	6,1	62,9
16		4'-OC_2H_5	CH_3	10 20	17,2 29,8	10 20	12,2 30,1
17		4'-Cl	CH_3	10 20	21,4 31,5	10 20	18,6 40,1
1	2	3	4	5	6	7	8
18		H	H	20	10,3	20	24,2
19		2'-CH_3	CH_3	20	17,1	20	39,4
20		4'-CH3	CH_3	20	14,6	20	21,3
21		3',4'-$(CH_3)_2$	C_4H_9-н	20	0	20	9,2
22		4'-CH_3	C_3H_7-i	20	31,4	20	48,7
23		4'-OC_2H_5	CH_3	20	18,2	20	27,4
24		2'-Cl	CH_3	20	15,5	20	37,4
25		4'-Cl	CH_3	20	9,4	20	29,9
26		2'-CH_3	CH_3	20	15,3	20	22,7
27		2'-CH_3	$(CH_2)_2OH$	20	9,8	20	27,2
28		4'-CH_3	CH_3	20	11,5	20	10,2
29		4'-CH_3	$(CH_2)_2OH$	20	29,7	20	40,2
30		3',4'-$(CH_3)_2$	CH_3	20	31,4	20	39,5
31		3',4'-$(CH_3)_2$	$(CH_2)_2OH$	20	34,8	20	35,9
32		4'-OC_2H_5	CH_3	20	10,6	20	15,3
33		4'-Cl	CH_3	20	12,4	20	19,6
Sodium diclofenac (DE_{50}=8 mg/kg)				-	37,5	-	-
Analginum (DE_{50}=55 mg/kg)				-	-	-	55

The minimization of the energy of all obtained conformers was implemented using force field MMFF94x and stopped when the root mean square gradient (RMS gradient) reached the value less than 0.01, with fixed number of conducted iterations no more than 200. Conformers, energy values of which exceeded the minimum found energy value for the given compound more than 7 kcal/mol, were excluded from the database as energetically unfavorable. Herewith, the maximum number of generated conformers for each compound was set at 200. Thus the base with 2545 conformers for 33 investigated compounds was formed. A previous optimization of the receptors structure included calculating partial charges on the atoms and the procedure of 3D protonation at pH=7.4, which aims to establish and correct the state of the ionization of acidic and basic functional groups in the residues of certain amino acids and also the position of the hydrogen atoms in the structure of peptide macromolecule.

3D protonation function allows to automatically optimizing the orientation of the hydrogen atoms so as to increase the possibility of forming hydrogen bonds by them and simultaneously minimize the total energy.

After that the final gradient minimization of energy with overlaying force field AMBER99 till RMS gradient achieved the value of 0.01 was conducted. In the active center of the receptor «artificial atoms» ("dummy atoms") were created and the amino acids residues (alpha centers) were selected within a radius of 4.5 Å from them. The determination of possible positions of the ligands in the active center of the receptor was carried out using an iterative procedure; in which randomly selected conformer was housed in the binding site in a way that the superposition of 3 arbitrary atoms of the ligand and three alpha centers of the receptor took place.

RESULTS AND DISCUSSION

According to the results of the conducted molecular docking the values of four scoring functions were calculated that allow to evaluate the stability of complexes formed between the ligands and corresponding receptors, and predict the ability of the synthesized substances to inhibit the catalytic activity of enzymes. A scoring function Affinity dG Scoring determines an *enthalpic* contribution to the value of the free energy of binding. A scoring function Alpha HB Scoring is calculated as a linear combination of two values, the first of which determines the geometric arrangement of the ligand in the active center of the acceptor, and the second - the effects of the formation of hydrogen bonds between them. A scoring function London dG Scoring determines the free energy of binding for a certain conformational position of the ligand. A scoring function GBVI/WSA dG Scoring determines the free energy of binding for a certain conformational position of the ligand and is calculated using force fields MMFF94x and AMBER99.

Values of the calculated scoring functions for complexes formed by the molecules of the synthesized substances and the receptors of COX-1 and COX-2, are shown in Tables 2 and 3, respectively.

Table 2: The results of the flexible molecular docking of the synthesized compounds to the COX-1 receptor (pdb code 1Q4G)

Compound code	GBVI/WSA dG	London dG	Alpha HB	Affinity dG
1	31,575	-1,16,610	-12,19,961	-35,530
2	35,930	-86,432	-12,44,849	-57,089
3	66,019	-88,464	-14,35,411	-30,475
4	13,541	-88,999	-12,28,994	-40,680
5	67,921	-88,245	-14,08,087	-43,821
6	55,239	-1,13,168	-12,09,576	-33,077
7	15,433	-1,04,598	-10,85,081	-48,207
8	56,464	-80,198	-13,44,016	-35,854
9	57,350	-86,790	-13,03,342	-33,122
10	34,408	-82,644	-13,83,793	-59,791
11	29,856	-68,939	-15,24,796	-42,967
12	-31,188	-86,782	-12,16,516	-44,867
13	0,6785	-84,100	-14,25,452	-39,155
14	50,013	-73,318	-13,56,127	-46,081
15	62,469	-84,174	-13,46,355	-45,163
16	22,769	-64,886	-12,17,101	-70,256
17	97,750	-1,12,181	-13,47,181	-17,006
18	27,443	-87,903	-12,27,431	-44,521
19	92,824	-83,972	-12,28,760	**-33,730**
20	54,185	-1,06,476	-13,59,627	-42,925
21	78,021	-83,779	-14,04,840	-49,621
22	34,851	-81,269	-14,52,366	-60,333
23	78,376	-1,05,775	-13,37,763	-48,277
24	29,553	-82,331	-13,47,737	-57,236
25	85,826	-82,858	-12,45,634	-45,273
26	53,320	-73,480	-14,06,523	-50,575
27	92,871	-66,957	-14,71,549	-36,143
28	-41,798	-85,192	-11,87,837	-48,865
29	47,111	-75,078	-16,58,895	-59,530
30	86,985	-68,103	-13,49,640	-44,886
31	18,797	-67,143	-13,82,815	-42,713
32	1,69,195	-73,286	-12,93,218	-32,794
33	1,03,814	-94,660	-13,09,648	-37,420
Diclofenac sodium	-0,6979	-1,05,624	-9,57,075	-60,407
Metamizole sodium	-21,613	-76,155	-9,03,362	-58,281
2-(1,1'-diphenyl-4-yl)propionic acid	-76,663	-1,39,861	-10,28,187	-77,516

Table 3: The results of the flexible molecular docking of the synthesized compounds to the COX-2 receptor (pdb code 3NT1)

Compound code	GBVI/WSA dG	London dG	Alpha HB	Affinity dG
1	-37,227	-97,129	-12,40,336	-76,256
2	-51,955	-97,525	-10,99,260	-38,522
3	-52,206	-94,498	-12,47,324	-39,868
4	-45,503	-1,01,588	-11,28,133	-46,538
5	-57,414	-1,15,971	-10,74,345	-58,766
6	-51,926	-1,05,776	-11,48,582	-39,635
7	-54,579	-1,05,904	-12,21,171	-42,298
8	-50,152	-99,588	-11,37,230	-39,656
9	-49,700	-99,292	-11,56,588	-39,468
10	-54,488	-95,466	-11,80,045	-53,194
11	-44,472	-97,458	-10,18,334	-58,676
12	-37,114	-91,819	-11,03,956	-52,290
13	-59,451	-98,244	-11,73,582	-60,594
14	-60,096	-1,04,711	-11,32,170	-54,543
15	-64,466	-94,861	-11,92,825	-56,401
16	-30,379	-98,785	-13,09,274	-65,074
17	-47,926	-97,365	-10,77,112	-60,094
18	-46,975	-93,838	-10,57,975	-38,385
19	-40,864	-98,107	-9,92,638	-47,112
20	-35,845	-1,07,870	-12,51,166	-51,976
21	-57,958	-91,315	-13,68,948	-59,464
22	-58,609	-1,04,915	-11,81,374	-55,492
23	-58,281	-1,01,154	-12,29,073	-48,132
24	-51,802	-88,648	-11,51,511	-45,010
25	-53,610	-93,500	-11,16,978	-45,207
26	-44,386	-90,164	-11,08,822	-64,247
27	-57,522	-80,950	-12,07,212	-61,735
28	-50,038	-98,433	-10,51,774	-62,032
29	-66,057	-1,02,926	-12,12,017	-61,171
30	-41,505	-90,982	-14,10,577	-64,091
31	-60,214	-87,581	-12,90,063	-59,952
32	-53,276	-91,569	-11,77,806	-57,330
33	-61,528	-1,04,858	-10,94,198	-59,230
Diclofenac sodium	-39,428	-92,298	-10,74,595	-73,823
Metamizole sodium	-41,712	-87,040	-9,86,251	-63,531
Naproxen	-72,959	-1,39,041	-9,45,634	-60,959

The calculated values of the scoring functions for the most energetically favorable conformation positions of the molecules of the investigated substances in the active centers of the mentioned enzymes indicate the possibility of the manifestation of the inhibitory activity by the synthesized substances relatively to both isoforms of cyclooxygenase which is shown non-selectively.

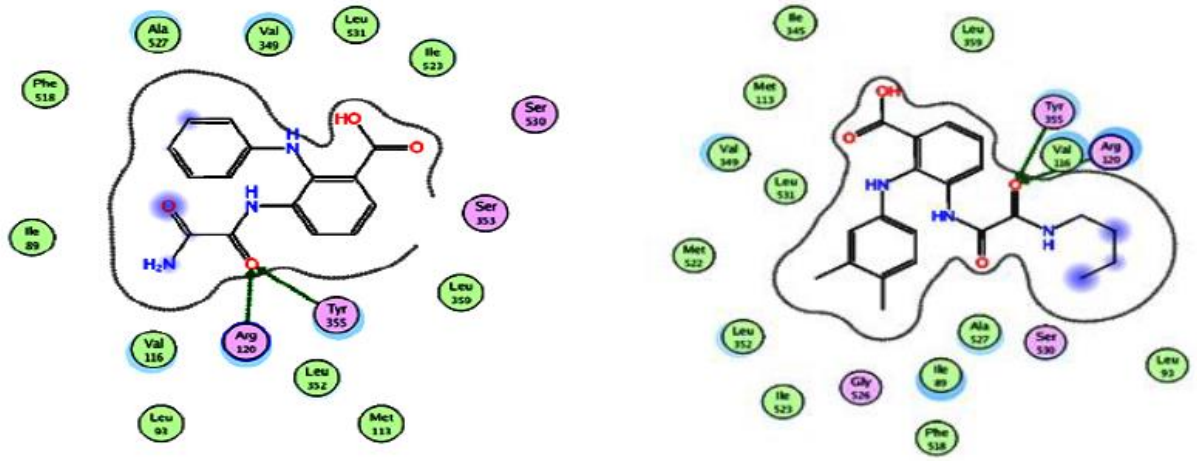
The values of the scoring function London dG, that determines the free energy of binding, in the case of complexes with COX-1, have higher absolute values almost for all synthesized compounds than in the case of complex COX-1 with analginum and the value of this function for 6 compounds is higher than for voltaren. The values of the scoring function GBVI/WSA dG have positive values almost for all investigated compounds. The absolute values of the scoring function Alpha HB for all compounds in complexes with COX-1 exceed the values of these functions for analginum, voltaren and 2-(1,1'-diphenyl-4-yl)propionic acid. However, the values of the scoring function Affinity dG for the investigated compounds are inferior to the values of this function for standard substances in absolute values; only for some compounds in complexes with COX-1 these values are somewhat higher.

Thus, it can be assumed that the inhibitory activity of the synthesized compounds relatively to COX-1 can be realized through the formation of complexes between them, the stability of which is provided mainly by energy-favorable geometric arrangement of the ligands in the active center of the acceptor, the formation of hydrogen bonds between them, the thermodynamic likelihood of such binding is confirmed by the negative values of the free energy scoring function London dG.

The values of the scoring functions that determine the free energy of binding (London dG and GBVI/WSA dG), in the case of complexes with COX-2, have negative values for all compounds. The values of London dG for all investigated substances are comparable or exceed the value of the respective scoring function for Voltaren and analginum, but are slightly inferior to the values of this function for naproxen. For 12 compounds the value of function GBVI/WSA dG is comparable with the same values for COX-2 complexes with voltaren and analginum, for all other compounds the absolute values of this function are higher, but lower compared to naproxen.

It should also be noted that despite the comparability of the values of the scoring function London dG for complexes formed by the synthesized compounds with COX-1 and COX-2, the values of the scoring function GBVI/WSA dG have generally higher absolute values in the case of complexes with COX-2, and this is the evidence of higher thermodynamic probability of the display of the inhibitory activity of the investigated substances in relation exactly to this COX isoform. The analysis of the geometric arrangement of the molecules of the synthesized substances in the active centers of COX-1 and COX-2, the types of binding and amino acids residues of side chains of peptides macromolecules that form bonds with the ligands was conducted.

It was found that the molecules of 3-oxamoyl*substituted* N-phenylanthranilic acids are able to bind to complexes with COX-1 by forming hydrogen bonds between one of the carboxyl oxygen atoms of the oxalic acid residue, that are H-acceptors (electron pair donors), Arg120 and Tyr355, herewith Arg120 can form as one as two bonds (compound 1, 3-5, 8-9). The diagrams of the ligands interactions with COX-1 for compounds 1 and 5, describing the nature and location of formed bonds, presented in Figure 1. For compound 7 two hydrogen bonds are formed between the carbonyl oxygen atoms of oxalyl and Arg120. Moreover, in the complexes COX-1 with the molecules of compounds 7 and 8 additional hydrogen bonds are formed by the hydroxyl or carbonyl oxygen atom of the carboxyl group of anthranilic acid and Arg83 or Ser530, respectively. The superposition of 2-(1,1'-diphenyl-4-yl)propionic acid and compound 8 in the active center of COX-1 is shown in Figure 2.



(a) (b)

Figure 1: The diagrams of the ligands interactions in complexes with COX-1 for compounds 1 (a) and 5 (b)

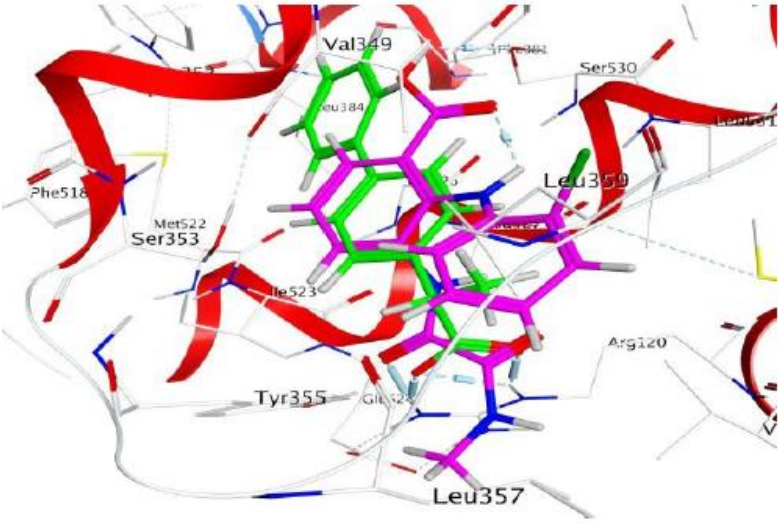
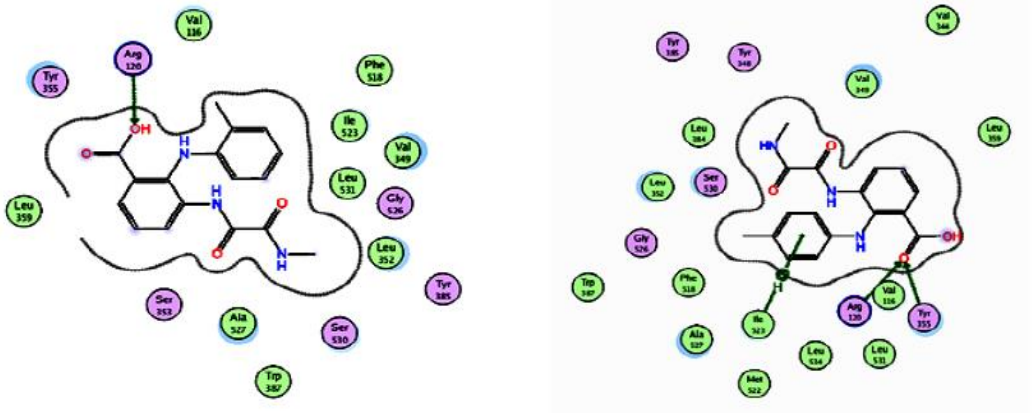


Figure 2: The superposition of 2-(1,1'-diphenyl-4-yl)propionic acid (green) and compound 8 (lilac) in the active center of COX-1

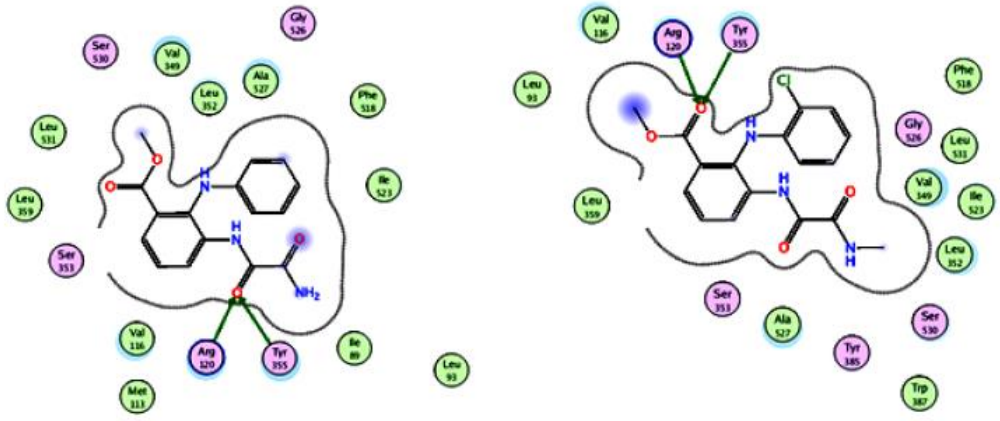
The formation of complexes with COX-1 by the molecules of compounds 2 and 6 is implemented by a hydrogen bond between the oxygen atom of the carboxyl group of anthranilic acid (for compound 2 it is the carbonyl and for compound 6–hydroxyl oxygen atom) and Arg120 (Figure 3).



(a) (b)

Figure 3: The diagrams of the ligands interactions in complexes with COX-1 for compounds 2 (a) and 6 (b)

Similarly, some synthesized methyl esters of 3-oxamoyl*substituted* N-phenylanthranilic acids form complexes with COX-1 by two hydrogen bonds between the carbonyl oxygen atom of aminooxalyl substituent and Arg120 and one bond between the same oxygen atom and Tyr355 (compounds 18 -22) (Figure 4).



a) b)

Figure 4: The diagrams of the ligands interactions in complexes with COX-1 for compounds 18 (a) and 24 (b)

The superposition of the molecules of compounds 8 and 14 in the active center of COX-1 is shown in Figure 5.

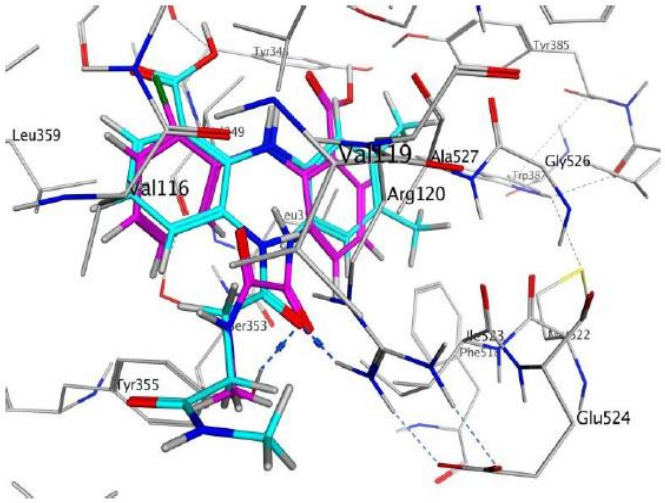
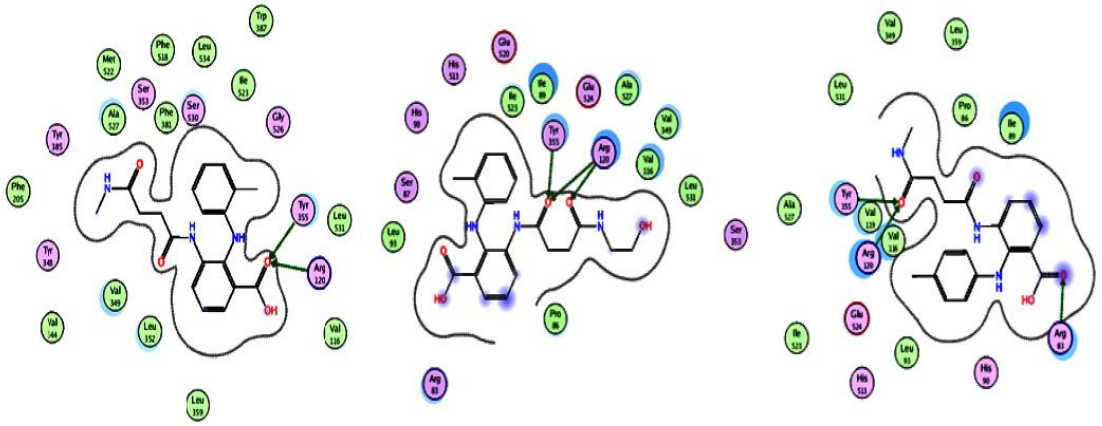


Figure 5: The superposition of the molecules of compounds 8 (lilac) and 14 (blue) in the active center of COX-

For compounds 23-25 the formation of complexes between their molecules and COX-1 is possible due to the formation of one or two hydrogen bonds between the hydroxyl oxygen atom of the carboxyl group of anthranilic acid and Arg120. For compound 24 the same oxygen atom forms one more bond with Tyr355 (Figure 4).

The molecules of 3-succinoyl*substituted* N-phenylanthranilic acids are capable of binding with COX-1 by forming one or two hydrogen bonds between the carbonyl oxygen atom of carbamoyl and Arg120. The said type of interactions is implemented in COX-1 complexes with compounds 12, 13, 15 and 16 (Figure 6). In complexes with compounds 12 and 13 the same oxygen atom forms a bond also with Tyr355. The molecule of compounds 12, moreover, forms an additional hydrogen bond between the hydroxyl oxygen atom of the carboxyl group of anthranilic acid and Arg83.



a) b) c)

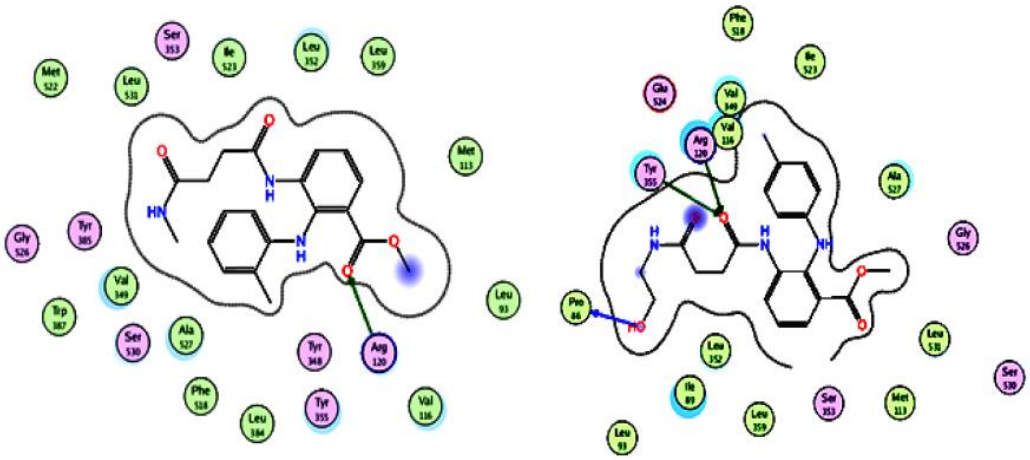
Figure 6: The diagrams of the ligands interactions in complexes with COX-1 for compounds 10 (a) and 11 (b), 12 (c)

In the complex of compound 11 with COX-1 hydrogen bonds are formed between Arg120 and two carbonyl oxygen atoms of the succinic acid residue, and also the bond between Tyr355 and the oxygen atom of carbamoyl (Figure 6). Compounds 14 and 17 form complexes with COX-1 by forming hydrogen bonds between Arg120 and Tyr355 and the carbonyl oxygen atom of propionylamino group in the third position of N-phenylanthranilic acid. For compound 10, by-one bond is formed between the hydroxyl oxygen atom of anthranilic acid, Arg120 and Tyr355 (Figure 6).

The formation of complexes with COX-1 by hydrogen bonds between the hydroxyl oxygen atom of the carboxyl group of anthranilic acid and Arg120 (compounds 26 and 32) (Figure 7) or between the carbonyl oxygen atom of aminocarbonyl group and

Arg120 and Tyr355 (compounds 27 and 28) is characteristic for the methyl esters of 3-succinoyl*substituted* N-phenylanthranilic acids.

For compounds 29-31 and 33 complexes are formed by hydrogen bonds between the oxygen atom of propionylamino group and Arg120 (Figure 7), and for compounds 29 and 33 even with Tyr355. Moreover, the complex of compound 29 with COX-1 is stabilized by the formation of the bond between Pro86 and the hydroxyl oxygen atom of aminocarbonyl substituent.



a) b)

Figure 7: The diagrams of the ligands interactions in complexes with COX-1 for compounds 26 (a) and 29 (b)

The superposition of molecules of compounds 22 and 29 in the active center of COX-1 is shown in Figure 8.

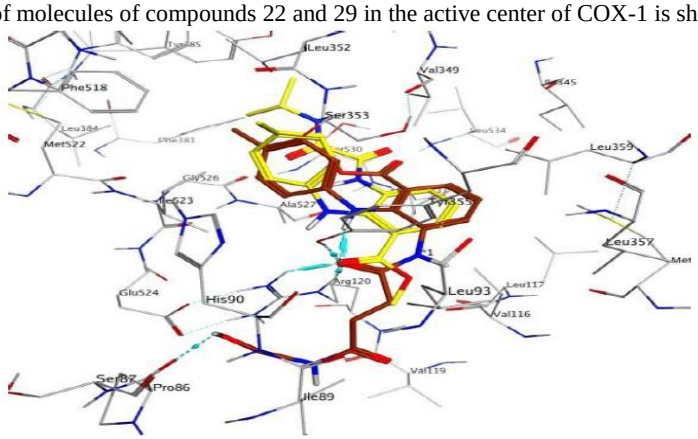
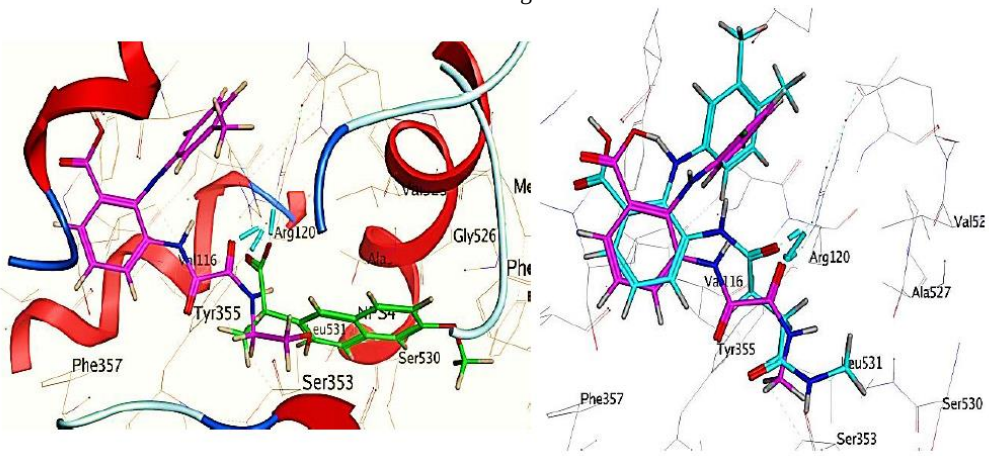


Figure 8: The superposition of molecules of compounds 22 (yellow) and 29 (brown) in the active center of COX-1

In the complexes formed by the molecules of 3-oxamoyl*substituted* N-phenylanthranilic acids and their methyl esters with COX-2, the presence of one or two hydrogen bonds is observed between the amino acid residue of Arg120 and the carbonyl oxygen atom of aminooxalyl substituent. Only in the complexes of compounds 1 and 20 with COX-2 the bonds are formed between Arg120 and the carbonyl oxygen atom of the carboxyl group of anthranilic acid, and for compound 1 one more hydrogen bond is formed between His90 and the nitrogen atom of aminooxalyl. The superposition of naproxen and the molecule of compound 3 and also the molecules of compounds 3 and 14 in the active center of COX-2 is shown in Figure 9.

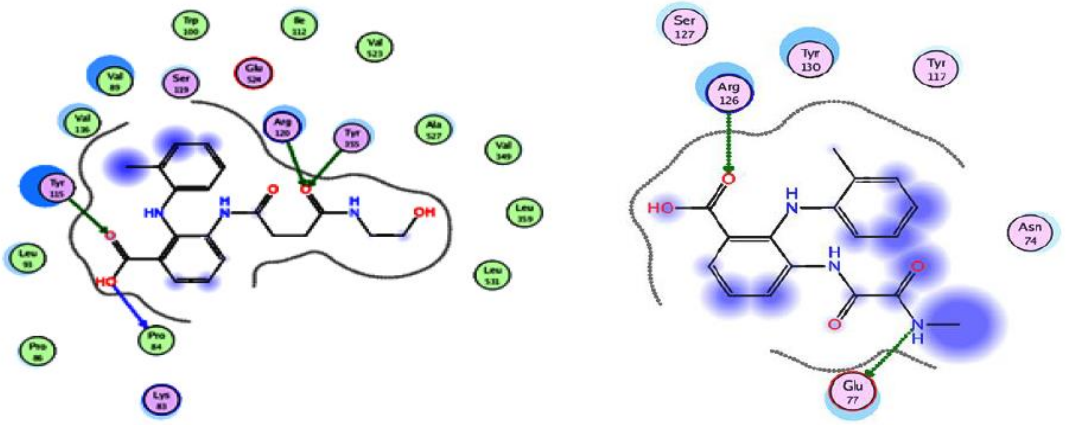


a) b)

Figure 9: The superposition of naproxen (green) and the molecule of compound 3 (lilac) (a) and the molecules of compounds 3 (lilac) and 14 (blue) in the active center of COX-2

The molecules of 3-succinoyl*substituted* N-phenylanthranilic acids and their methyl esters bind to COX-2 by forming one or two hydrogen bonds between one of the carbonyl oxygen atoms of aminocarbonyl or propionylamino group and Arg120 and Tyr355. In the complexes formed by the given receptor with the molecules of compounds 11, 17 and 26, apart from the above mentioned types of binding, by-one more hydrogen bond is formed between the carbonyl oxygen atom of the carboxyl group of anthranilic acid and Tyr115 (Figure 10), and for compound 11, moreover, one more bond between the hydroxyl oxygen atom of the same group and Pro84. An additional stabilization of the complex of compound 31 with COX-2 is implemented by π-H interaction between the aromatic ring of anthranilic acid and Leu93. Only in the complex of compound 16 with COX-2 (Figure 10) bonds are formed between the carboxyl and hydroxyl oxygen atoms of the carboxyl group of anthranilic acid and Arg120 and Ser119, respectively.

The superposition of the molecules of compounds 22 and 29 in the active center of COX-2 is shown in Figure 11.



a) b)

Figure 10: The diagrams of the ligands interactions in complexes with COX-2 for compounds 11 (a) and 16 (b)

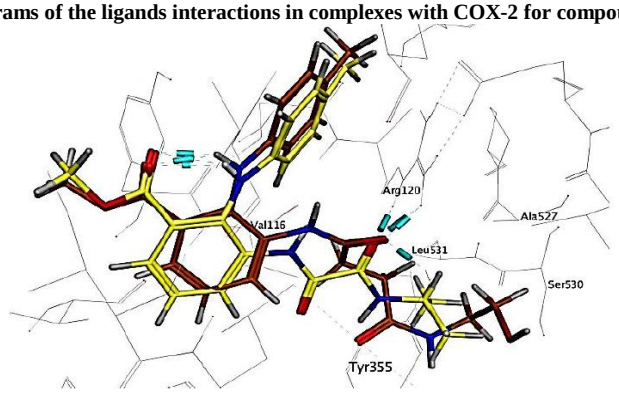


Figure 11: The superposition of the molecules of compounds 22 (yellow) and 29 (brown) in the active center of COX-2

Table 4 shows the types, energy and localization of the molecules interactions of 3-oxamoyl*substituted and* 3-succinoyl*substituted* N-phenylanthranilic acids and their methyl esters, that show the highest anti-inflammatory and analgesic activity, in complexes with COX-1 and COX-2.

Table 4: The amino acids residues of the active center of the receptor, types and energy of interactions in the complexes of 3-oxamoyl*substituted and* 3-succinoyl*substituted* N-phenylanthranilic acids and their methyl esters with COX-1 and COX-2

Compound code	COX-1				COX-2			
	The atoms of the investigated compounds that interact with the receptor	Amino acids residues and types of bonds	Bond lengths, Å	Interaction energy, kcal/mol	The atoms of the investigated compounds that interact with the receptor	Amino acids residues and types of bonds	Bond lengths, Å	Interaction energy, kcal/mol
1	2	3	4	5	6	7	8	9
3	Carbonyl O of oxalyl *Ph*-NH-CO-	Arg120 hydrogenous	2.61	-2.7	Carbonyl O of oxalyl -C(O)-NH-	Arg120 hydrogenous	2.61	-3.9
	Carbonyl O of oxalyl *Ph*-NH-CO-	Tyr355 hydrogenous	2.34	6.4	–	–	–	–
4	Carbonyl O of oxalyl -C(O)-NH-	Arg120 hydrogenous	2.86	-5.6	Carbonyl O of oxalyl -C(O)-NH-	Arg120 hydrogenous	2.56	-2.9
8	Carbonyl O of oxalyl *Ph*-NH-CO-	Arg120 hydrogenous	2.60	-2.8	Carbonyl O of oxalyl -C(O)-NH-	Arg120 hydrogenous	2.67	-1.9
	Carbonyl O of oxalyl *Ph*-NH-CO-	Tyr355 hydrogenous	2.43	2.2	Carbonyl O of oxalyl -C(O)-NH-	Arg120 hydrogenous	2.69	-3.8
	Hydroxyl O of the carboxyl group of anthranilic acid -COOH	Ser530 hydrogenous	2.62	-0.6	–	–	–	–
14	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Arg120 hydrogenous	2.48	2.3	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Arg120 hydrogenous	2.48	1.7
	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Tyr355 hydrogenous	2.64	-0.7	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Tyr355 hydrogenous	2.66	-1.4
15	Carbonyl O of carbamoyl R^1NH-C(O)-	Arg120 hydrogenous	3.39	-0.8	Carbonyl O of carbamoyl R^1NH-C(O)-	Arg120 hydrogenous	3.00	-5.1
	–	–	–	–	Carbonyl O of carbamoyl R^1NH-C(O)-	Tyr355 hydrogenous	2.99	-1.1
22	Carbonyl O of the carboxyl group of anthranilic acid -COOH	Arg83 hydrogenous	2.75	-1.4	Carbonyl O of carbamoyl R^1NH-C(O)-	Arg120 hydrogenous	2.70	-2.7
	Carbonyl O of the carboxyl group of anthranilic acid -COOH	Arg120 hydrogenous	2.59	-5.4	Carbonyl O of carbamoyl R^1NH-C(O)-	Arg120 hydrogenous	2.75	-2.9
	Carbonyl O of the carboxyl group of anthranilic acid – $COOCH_3$	Tyr355 hydrogenous	2.77	-1.3	–	–	–	–
29	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Arg120 hydrogenous	2.70	-1.8	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Arg120 hydrogenous	2.48	2.0
	Carbonyl O of	Arg120	2.69	-5.1	Carbonyl O	Tyr355	2.64	-1.5

	propionylamino-group *Ph*-NH-CO-	hydrogenous			of propionylamino-group *Ph*-NH-CO-	hydrogenous		
	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Tyr355 hydrogenous	2.90	-1.3	–	–	–	–
	Hydroxyl O of aminocarbonyl substituent -NH-$(CH_2)_2$-OH	Pro86 hydrogenous	3.10	-0.9	–	–	–	–
30	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Arg120 hydrogenous	2.57	-1.1	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Arg120 hydrogenous	2.45	5.2
	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Arg120 hydrogenous	2.81	-2.4	Carbonyl O of propionylamino-group *Ph*-NH-CO-	Tyr355 hydrogenous	2.58	-0.1

CONCLUSION

1. The results of the conducted flexible molecular docking of the derivatives of N-phenylanthranilic acid to COX-1 and COX-2 show the possibility of the formation of stable complexes between them, in which the location of ligands in the active center of the receptor and the amino acids residues of side chains, involved in the formation of non-covalent bonds, are analogical to the geometry and types of binding of classic nonsteroidal anti-inflammatory drugs, established basing on the crystallographic studies.
2. For all investigated compounds binding between the ligand and mentioned receptors is realized by the formation of hydrogen bonds involving oxygen atoms of the carboxyl group of anthranilic acid or the carbonyl oxygen atoms of the residues of dicarboxylic acids in the third position of phenylanthranilic acid.

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