A MOLECULAR DOCKING OF NEW 9β-HALOGENATED PROSTAGLANDINE ANALOGUES

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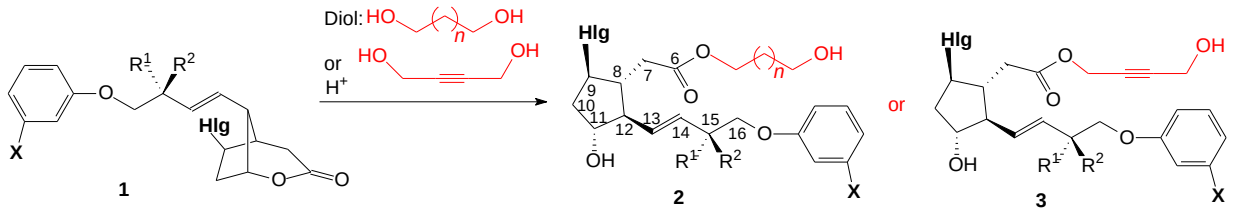
Prostaglandins with cytoprotective activity were studied for a long time and a few PGE_1 and PGE_2 stable analogues were promoted as drugs: arbaprostil, enprostil, misoprostol and rioptostol; the same activity has nocloprost, a 9β-chlorine prostaglandin analogue, and many 9β- ar 11β-substituted prostaglandins were synthesized and studied for their biological activity. In the same direction we have synthesized 9β-halogenated prostaglandins of type **2** and **3**, starting from the δ-lactone compound **1** with diols (n = 0 to 4) or 2-butyn-1,4-diol, catalyzed by toluenesulfonic acid [1, 2] (Scheme 1):



2a, Hlg = Cl, X = Cl, *n* = 0
2b, Hlg = Cl, X = Cl, *n* = 1
2c, Hlg = Br, X = Cl, *n* = 1
2d, Hlg = F, X = Cl, *n* = 1
2e, Hlg = Cl, X = Cl, *n* = 2
2f, Hlg = Cl, X = CF_3, *n* = 2
2g, Hlg = Br, X = Cl, *n* = 2
2h, Hlg = F, X = Cl, *n* = 2
2i, Hlg = Cl, X = Cl, *n* = 3
2j, Hlg = Cl, X = Cl, *n* = 4
2k, Hlg = Cl, X = Cl, *n* = 2, R^1= OH, R^2 = H
2l, Hlg = Cl, X = CF_3, *n* = 2, R^1=OH R^2 =H

3a, Hlg = Cl, X = Cl, R^1, R^2 = O
3b, Hlg = Cl, X = CF_3, R^1, R^2 = O
3c, Hlg = Cl, X = Cl, R^1 = OH R^2 = H
3d, Hlg = Cl, X = CF_3, R^1 = OH R^2 = H

Scheme 1. Synthesis of 9β-halogenated prostaglandin analogues of type **2** and **3**.

The compounds have not only a 9β-halogen (Cl, Br and F in the Scheme 1), but also an ester group at the carbon atom 6 (PGs numbering). Such an ester group was presented in the literature and the compounds showed cytoprotective activity [3] and the compounds synthesized, presented in Scheme 1, are waiting to have also cytoprotective activity.

We have done a molecular docking study, using CLC Drug Discovery Workbench 2.4. software and an oxidoreductase enzyme receptor, chosen from the Protein Data Bank, ID: *4KEW*. (www.rcsb.org)**,** to put in evidence their *predicted* cytoprotective activity. In the study we use as standard two recognized drugs, *omeprazole* (co-crystallized with the enzyme) and *nocloprost*. The co-crystallized omeprazole with protein receptor was used for docking: defining the binding site and binding pockets, docking validation and to

identify hydrogen bonds between co-crystallized omeprazole and amino acid residues of receptor. Then the prostaglandin analog drug *nocloprost*, used as standard in the study, has been docked (a docking study about Nocloprost has not been found in the literature) and the results are presented in Table 1 (entry 2); docking pose of the interactions between nocloprost and the amino acid residues are presented in Fig. 1.

Table 1. Docking score and the molecular properties of ligands: omeprazole, nocloprost, 9β-halogenated prostaglandin analogs: **2a-2l** and **3a-3d**, calculated with CLC Drug Discovery Workbench 2.4 software.

Ligand	Score	RMSD*	Atoms No.	Weight	Flexible bonds	Lipinski violation	HD	HA	Log P
Omeprazole (co-crystallized)	**-58.11**	0.06	41	328.41	5	0	0	5	3.28
Nocloprost	**-71.25**	1.32	64	400.98	12	1	3	4	5.38
2a	*-66.93*	1.02	49	417.28	10	0	2	6	2.35
2b	-73.00	0.83	52	431.31	11	0	2	6	2.71
2c	*-70.67*	1.18	52	475.76	11	0	2	6	2.88
2d	-74.92	0.78	52	414.85	11	0	2	6	2.46
2e	-74.67	0.83	55	445,33	12	0	2	6	3.06
2f	-74.92	0.43	58	478.89	13	0	2	6	3.32
2g	*-67.73*	1.67	55	489.78	12	0	2	6	3.23
2h	-73.63	0.92	55	428.88	12	0	2	6	2.82
2i	-72.29	1.60	58	459.36	13	0	2	6	3.42
2j	*-71.13*	1.36	61	473.39	14	0	2	8	3.78
2k	-75.03	0.76	57	447.35	12	0	3	6	2.72
2l	-77.57	1.25	60	480.90	13	0	3	6	2.97
3a	-75.09	1.42	51	441.30	11	0	2	6	2.41
3b	-82.27	0.63	54	474.85	12	0	2	6	2.66
3c	-77.47	0.41	53	443.32	11	0	3	6	2.06
3d	-84.91	1.28	56	476.87	12	0	3	6	2.32

* RMSD: root-mean-square deviation; RMSD should be <2.

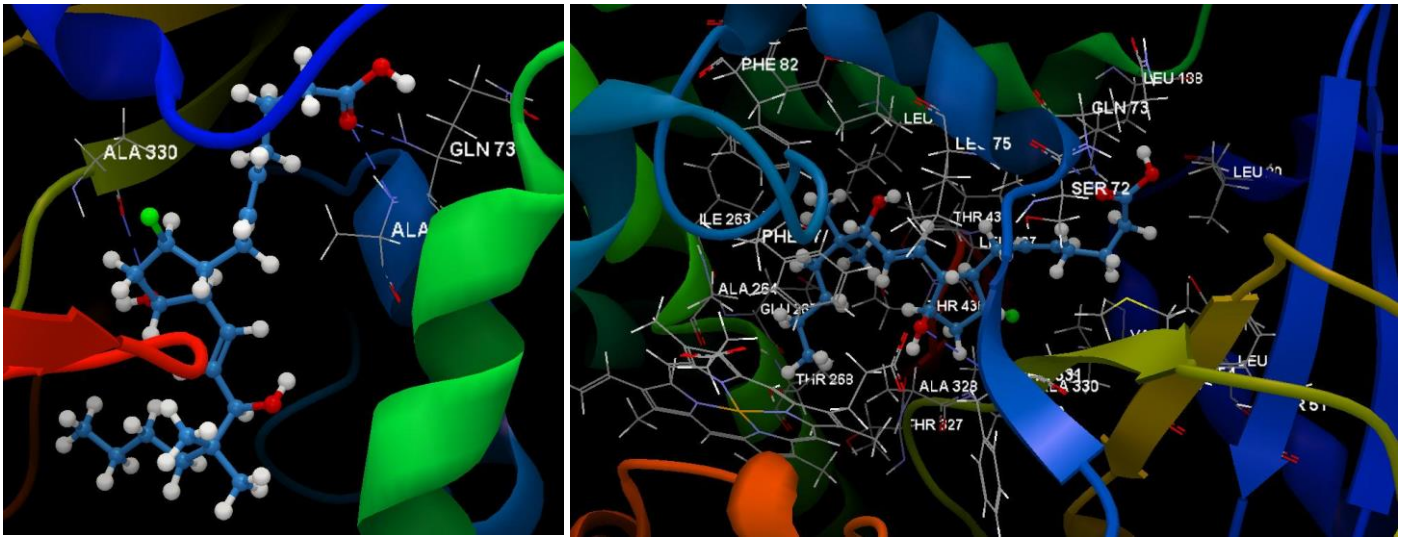


Figure 1. a) Hydrogen bonds between the amino acid residues ALA 330, GLN 73 and ALA 74 of the receptor and Nocloprost; b) Docking pose of Nocloprost ligand interacting with amino acid residues in the binding site

The 9β-halogenated prostaglandin analogs **2a-2l** and **3a-3d**, presented in Scheme 1, were finally docked and the results of the calculated properties (flexible bonds, Lipinski violations, the number of hydrogen bond donors, the number of hydrogen bond acceptors and log P) [4] are presented in Table 1 and Fig. 2. The calculated parameters *can predict* if a molecule possesses properties that might turn it into an active drug, according to the Lipinski's rule of five [4].

An expressive presentation of the docking score is presented in Fig. 2:

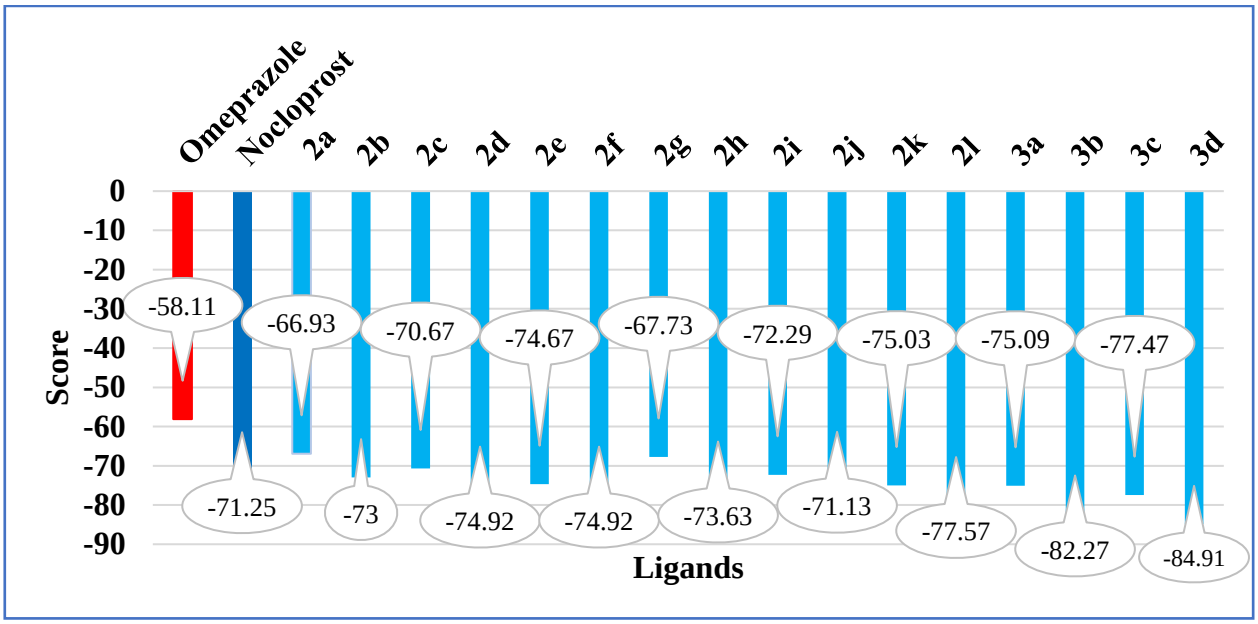


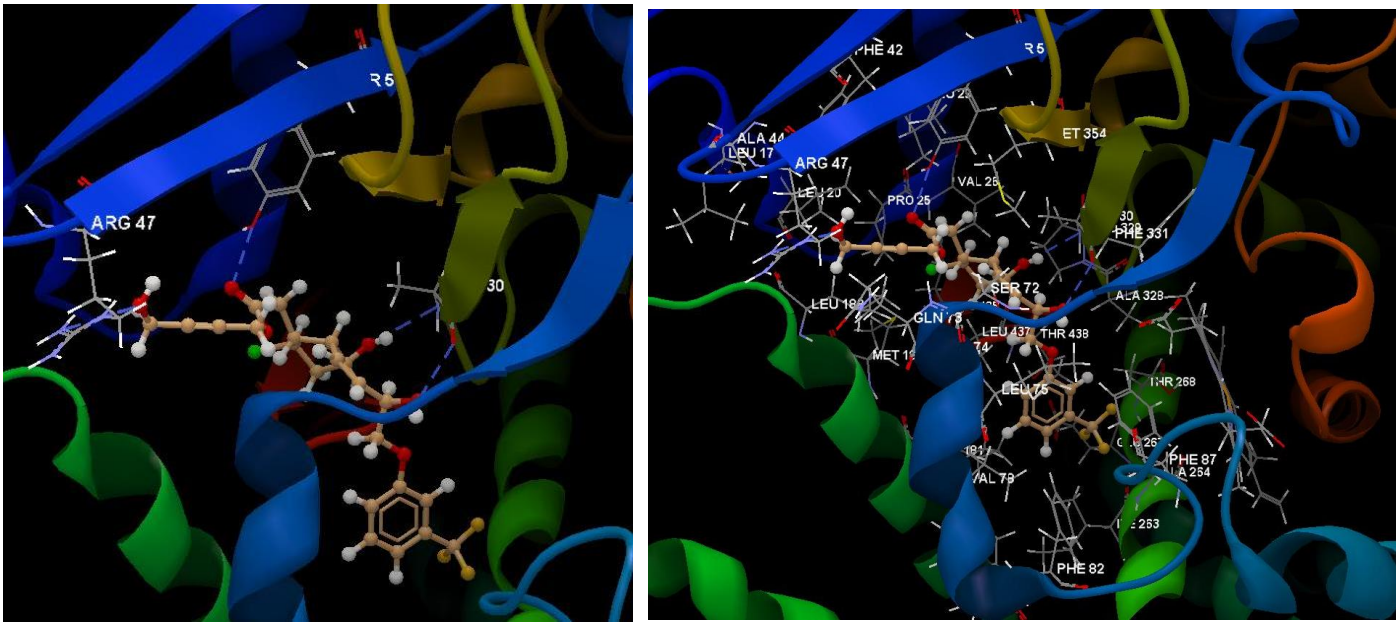
Figure 2. Docking score of the 9β-halogenated prostaglandin compounds **2a-2l** and **3a-3d** by comparison with the docking score of two cytoprotective (anti-ulcer) recognized drugs: omeprazole and nocloprost.

According to the data presented in Table 1, all 9β-halogenated compounds comply with the Lipinski rules (Lipinski violation is 0), and nocloprost drug have one violation. In Table 1, the docking score (and RMSD, which is < 2) is also presented. All 9β-halogenated analogs and nocloprost also have docking scores greater than that of omeprazole (-58.11, RMSD 0.06). The majority of the 9β-halogenated analogs have a docking score greater than that of 9β-chlorine nocloprost prostaglandin recognized drug (-71.25, RMSD 1.32), used as standard in the study, with the exception of the compounds **2a** (-66.93, RMSD 1.01), **2c** (-70.67, RMSD 0.83), **2g** (-67.73, RMSD 1.67) and **2j** (-71.13, RMSD 1.36) (Fig. 2). Basing on the docking score, the study shows that the *predicted* cytoprotective (anti-ulcer) activity of the compounds **2b**, **2d-2f**, **2h-2i**, **2k-2l**, **3a-3d** is greater than that of nocloprost. The compound **3d** had the best score (-84.91), followed by compound **3b** (-82.27), compounds with a 2-butyn synthon in α-side chain; for compounds with normal α-side chain, the best score is for the compound **2l** (-77.57).

Besides the parameters mentioned in Table 1, group interaction, hydrogen bonds of ligands with amino acid residues were determined and hydrogen bond length was calculated.

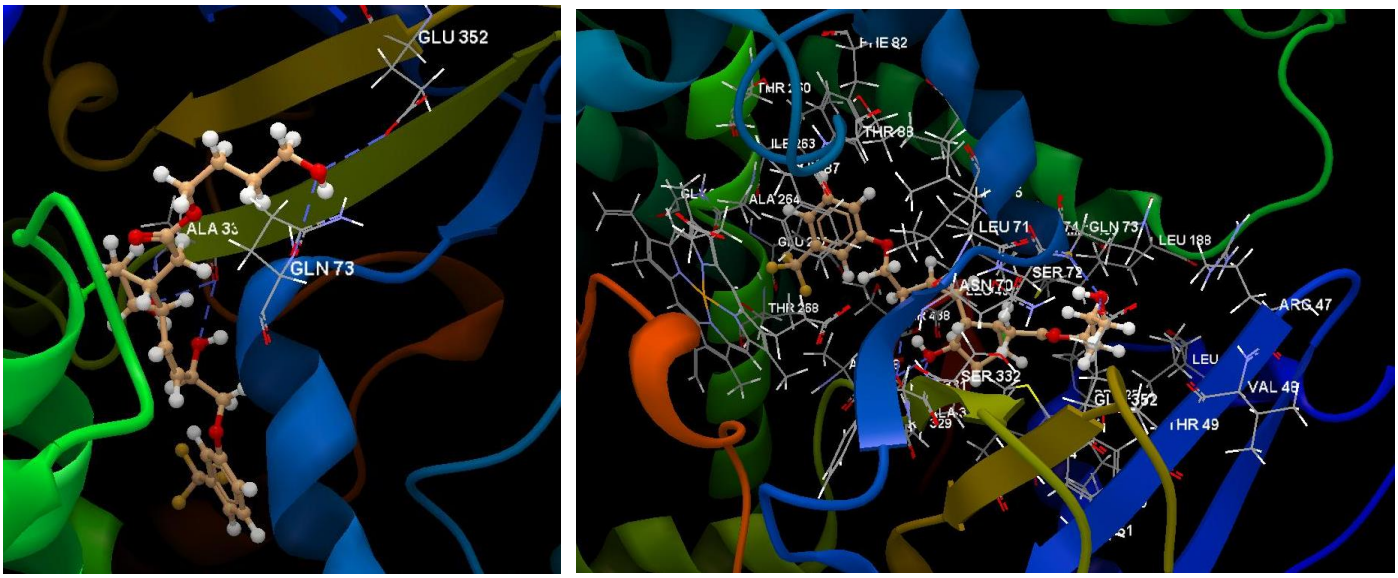
A few correlations between docking score and substituents on the prostaglandin skeleton have also been done.

The docking poses of the ligands with the best score interacting with the amino acid residues of the protein, with the 2-butyn scaffold **3d** and with linear chain in α-side chain **2l**, are presented in Fig. 3 and **3** Fig. 4:



a) b)

Figure 3. a) Hydrogen bonds between the residues of the ARG 47, TYR 51 and ALA 330, and the compound **3d**; b) Docking pose of the compound **3d** interacting with amino acid residues in the binding site.



a) b)

Figure 4. a) Hydrogen bonds between the residues of the ALA 330, GLN 73 and GLU 352 and the compound **2l**; b) Docking pose of the compound **2l** interacting with amino acid residues in the binding site.

References

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