proceedings

MDPI

Proceedings

A Molecular Docking of New 9β-Halogenated Prostaglandin Analogues †

Constantin I. Tanase *, Lucia Pintilie and Elena Mihai

National Institute for Chemical-Pharmaceutical Research and Development, Department of Bioactive Substances and Pharmaceutical Technologies, 112 Vitan Av., 031299 Bucharest-3, Romania; lucia.pintilie@gmail.com (L.P.); anele_drag@yahoo.com (E.M.)

* Correspondence: cvtanase@gmail.com

† Presented at the 23rd International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2019; Available online: https://ecsoc-23.sciforum.net/.

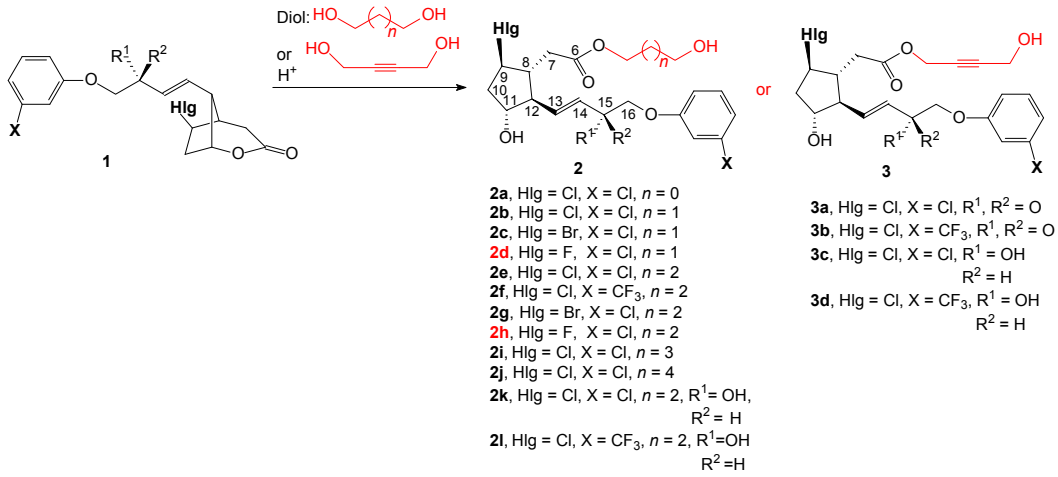
Published: 14 November 2019

Abstract: Prostaglandins (PGs) 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. Similarly, nocloprost, a 9β-chlorine prostaglandin analogue, and many 9β- and 11β-substituted prostaglandins were synthesized and studied for their biological activity. We previously synthesized new 9β-halogenated prostaglandins with an ester group at the carbon atom 6 (PGs numbering) by the reaction of a δ-lactone intermediate with diols in acid catalysis. These compounds were used in the current molecular docking study to determine their potential cytoprotective (anti-ulcer) activity. The current study was done with the CLC Drug Discovery Workbench 2.4. software and an oxidoreductase enzyme receptor, chosen from the Protein Data Bank, ID: 4KEW (www.rcsb.org). We used two recognized drugs, omeprazole (co-crystallized with the enzyme) and nocloprost, as the standard. The 9β-halogenated prostaglandin analogs were docked. Nocloprost and all 9β-halogenated compounds had docking scores greater than that of omeprazole. The majority of the 9β-halogenated analogs had docking scores even greater than that of nocloprost, indicating that these compounds could have potential cytoprotective (anti-ulcer) activity. A few correlations between docking score and substituents on the prostaglandin skeleton were found.

Keywords: 9β-halogenated prostaglandins; molecular docking study; cytoprotective; δ-lactone opening; diols; 1,4-butyndiol

Prostaglandins (PGs) 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. Similarly, nocloprost, a 9β-chlorine prostaglandin analogue, and many 9β- and 11β-substituted prostaglandins were synthesized and studied for their biological activity. In the same direction, we have synthesized 9β-halogenated prostaglandins of types 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).

The new 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). Other compounds with the same ester group have been presented in the literature and showed cytoprotective activity [3]; the new compounds synthesized as in Scheme 1 have not been tested for cytoprotective activity.



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

We completed a molecular docking study, using CLC Drug Discovery Workbench 2.4. software (QIAGEN Bioinformatics, Aarhus, Denmark) and an oxidoreductase enzyme receptor, chosen from the Protein Data Bank, ID: 4KEW (www.rcsb.org), to determine the predicted cytoprotective activity of the new compounds. In the study, we use as a standard two recognized drugs, omeprazole (co-crystallized with the enzyme) and nocloprost. The co-crystallized omeprazole with a protein receptor was used for docking, defining the binding site and binding pockets, validating docking, and identifying hydrogen bonds between co-crystallized omeprazole and amino acid residues of the receptor. Then, the prostaglandin analog drug nocloprost, also used as a standard in this study, was docked (no docking studies about nocloprost were found in the literature) and the results are presented in Table 1 (in red) docking poses of the interactions between nocloprost and the amino acid residues are presented in Figure 1.

Table 1. Docking scores and the molecular properties of the ligands omeprazole, nocloprost, and 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, **HD = hydrogen donors, ***HA = hydrogen acceptors.

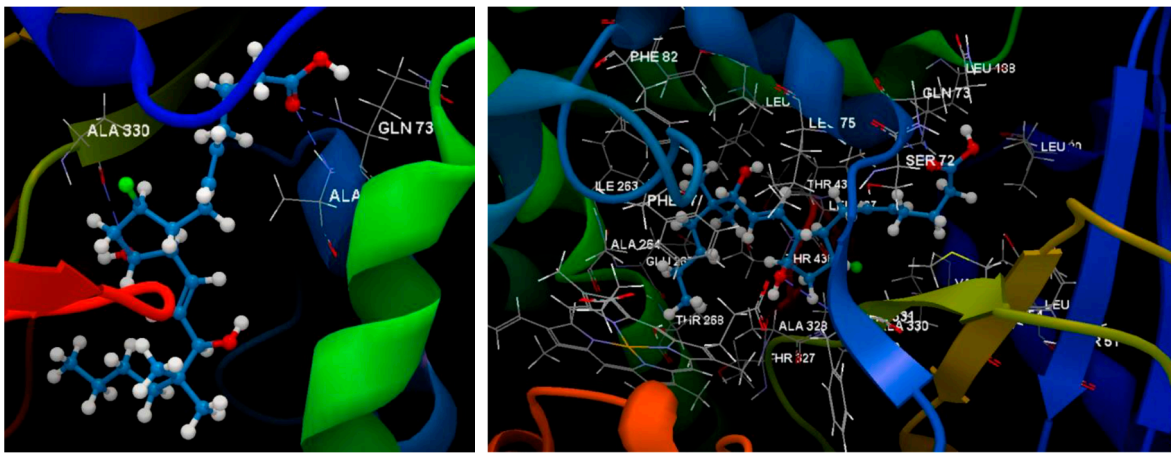


Figure 1. (**a**) Hydrogen bonds between the amino acid residues ALA 330, GLN 73, and ALA 74 of the receptor and nocloprost; (**b**) Docking pose of the nocloprost ligand interacting with amino acid residues in the binding site.

The 9β-halogenated prostaglandin analogs **2a–2l** and **3a–3d**, presented in Scheme 1, were 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 Figure 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 Figure 2.

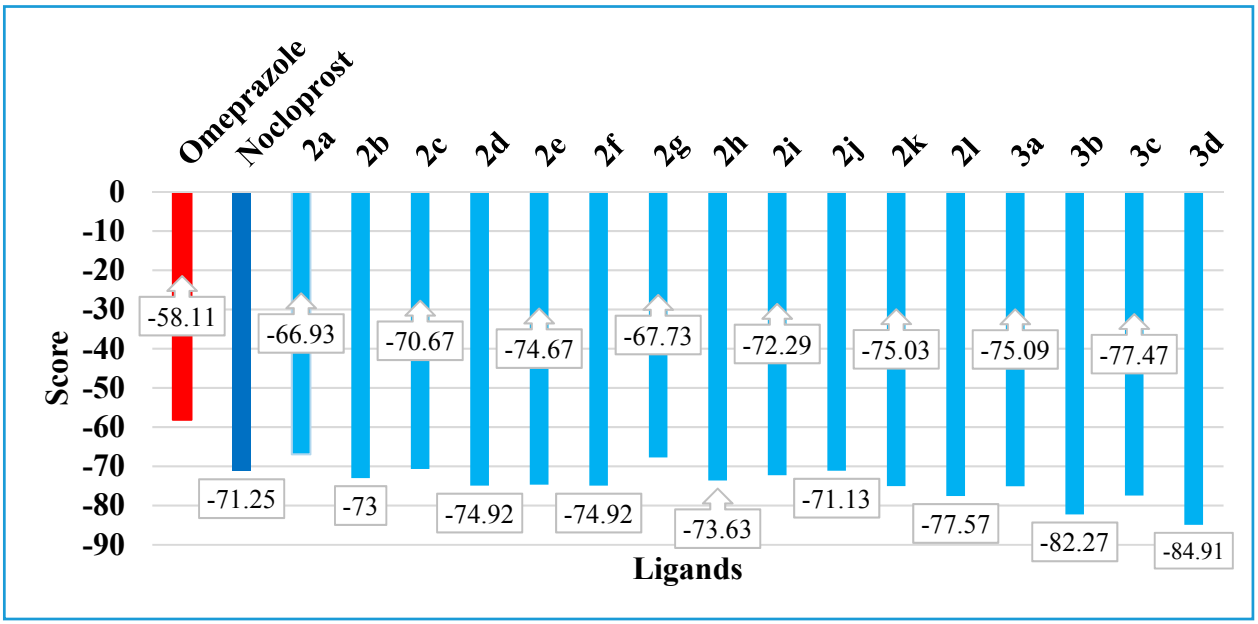


Figure 2. Docking score of the 9β-halogenated prostaglandin compounds **2a–2l** and **3a–3d** by comparison with the docking score of two cytoprotective (anti-ulcer)-recognized drugs: omeprazole and nocloprost.

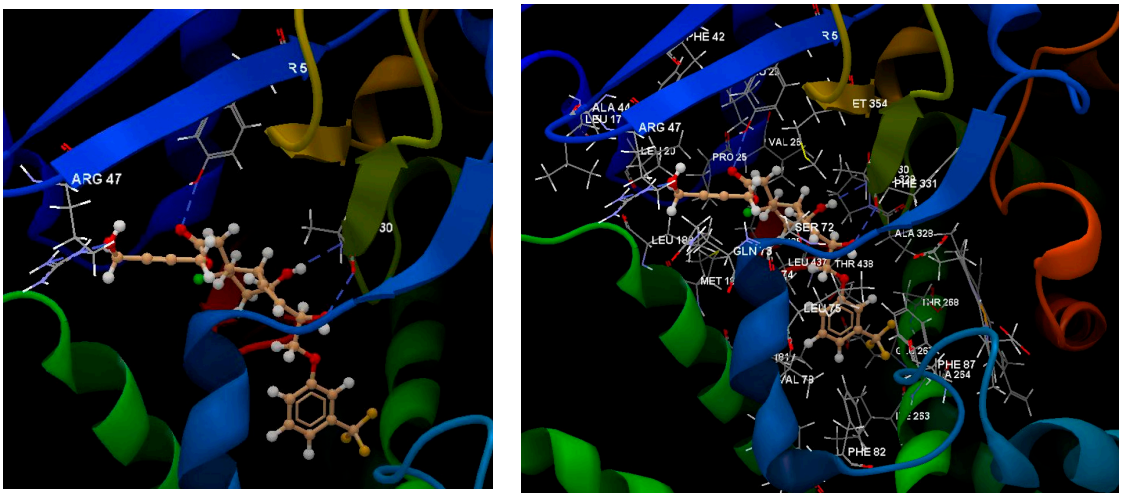
According to the data presented in Table 1, all 9β-halogenated compounds comply with the Lipinski rules (Lipinski violation is 0), and the nocloprost drug has one violation. In Table 1, the docking score and RMSD, which is <2, are also presented. All 9β-halogenated analogs and nocloprost have docking 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 the 9β-chlorine nocloprost prostaglandin-recognized drug (−71.25, RMSD 1.32), used as a 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) (Figure 2). Based on the docking scores, this study shows that the predicted cytoprotective (anti-ulcer) activities of the compounds **2b**, **2d–2f**, **2h–2i**, **2k–2l**, **3a–3d** are greater than that of nocloprost. The compound **3d** had the best score (−84.91), followed by compound **3b** (−82.27), both those compounds have a 2-butyn synthon in α-side chain; for compounds with a normal α-side chain, the best score is for the compound **2l** (−77.57).

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

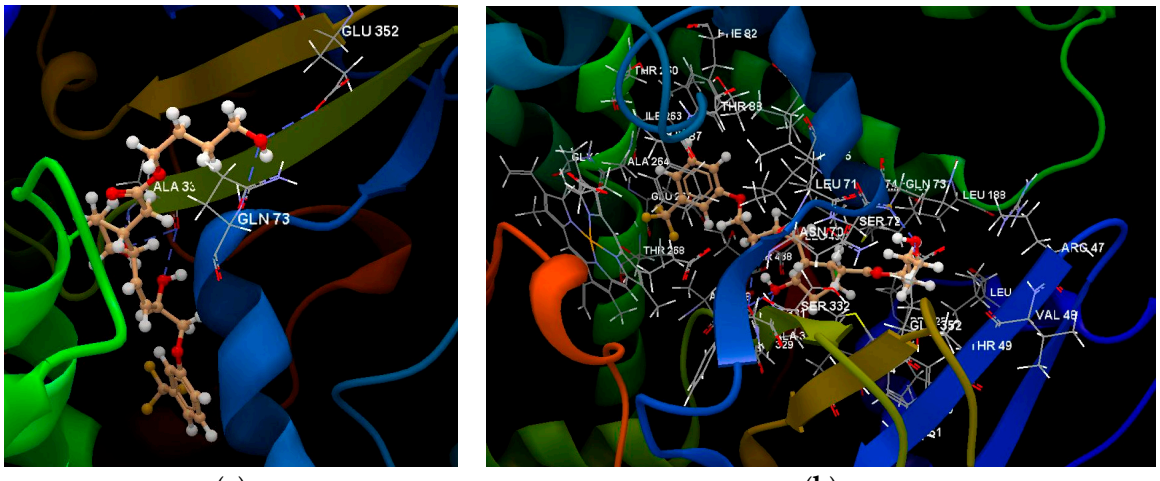
A few correlations between docking score and substituents on the prostaglandin skeleton were also found.

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



(**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

1. Tănase, C.; Cocu, F.; Drăghici, C.; Căproiu, M.T.; Maganu, M. New β-halogenated prostaglandine analogues with an ester group at C-6 of the α-side chain. *Rev. Chim. (Bucharest)* **2016**, *67*, 468–475.
2. Tănase, C.; Cocu, F.; Drăghici, C.; Căproiu, M.T.; Maganu, M. 9β-Halogenatedprostaglandin Compounds and Procedures for Their Preparation. Patent Request RO 129720 A2, 2013.
3. Konishi, Y.; Kawamura, M. Novel 5-hetero-6-oxo-PGE Derivatives. EP 0386901 A1, 1990.
4. Lipinski, C.A. Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discov. Today Technol.* **2004**, *1*, 337–341.