International Journal of Computational and Experimental Science and ENgineering (IJCESEN)

Vol. 9-No.2 (2023) pp. 81-85
http://dergipark.org.tr/en/pub/ijcesen

ISSN: 2149-9144

Research Article

Comparison of The Molecular Docking Properties of Three Potentially Active Agents

Güvenç GÖRGÜLÜ[1]*, Bülent DEDE[2]

[1]*Burdur Mehmet Akif Ersoy University, Faculty of Education, Department of Science Education, Burdur, Türkiye
* **Corresponding Author** : **Email:** guvencgorgulu@mehmetakif.edu.tr - **ORCID:** 0000-0003-4740-7265

[2]Süleyman Demirel University, Faculty of Arts and Science, Department of Chemistry, Isparta, Türkiye
Email: bulentdede@sdu.edu.tr - **ORCID:** 0000-0003-1416-7373

Article Info:

DOI: 10.22399/ijcesen.1147789
Received : 23 July 2022
Accepted : 07 June 2023

Keywords

Molecular Docking
VEGFR-2
COX-2
In-silico

Abstract:

Antineoplastic agents are generally the drugs used to recess or prevent tumor growth which is promoted in many cases by certain factors like vascular endothelial growth factor-2 (VEGFR-2) and cyclooxygenase-2 (COX-2). These two factors seem important in angiogenesis and lymphangiogenesis in fetal, normal and neoplastic tissue. Prevention of VEGF family of proteins and COX-2 enzyme is a good strategy to inhibit the growth of tumor tissue eventually may give rise to recession. In this study, three potentially active and an active ligand were tested for their binding properties to two target molecules mentioned above by molecular docking study. This research is aimed to compare three different molecules according to their binding affinities, binding energies and the nature of bonds formed between the ligand and the target molecules. Showing the 3D structures will localize the fitted ligands on proteins and the possible hydrogen bonds formed were defined. Among the three proposed ligands, Ligand 1 showed the closest results to the commercial product lenalidomide®. All three ligands showed similar ΔG values and fitness scores with lenalidomide® which is an indicator of good fit, proximity and orientation with the target molecule.

1. Introduction

Specific binding modes of ligands to the target molecules are one of the major concerns of pharmacology today. To understand the properties of these couples of ligand protein complexes in term of proximity and orientation would help the researchers to construct a pattern of molecular interaction. A scorable fitness related to the binding energy, length, type, number, strength and the localization of the bonds and other intermolecular interactions would make a great contribution to drug design studies [1]. Molecular docking is essentially the study of intermolecular interaction that has become an important component of computer aided drug design process [2-4]. In these aspects, molecular docking is an important pre-study for the elimination of candidate molecules. Antineoplastic agents are generally the drugs used to recess or prevent tumor growth which is promoted in many cases by certain factors like vascular endothelial growth factor-2 (VEGFR-2) and cyclooxygenase-2 (COX-2). These two factors seem important in angiogenesis and lymphangiogenesis in fetal, normal and neoplastic tissue. Prevention of VEGF family of proteins and cyclooxygenase-2 enzyme is a good strategy to inhibit the growth of tumor tissue eventually may give rise to recession [5-8]. In this study, three previously synthesized [9-11] potentially active ligands were tested for their binding properties to two synergistically active target molecules (VEGFR-2 and COX-2) by molecular docking study. It is aimed to compare three different molecules according to their binding affinities, binding energies and the nature of bonds formed between the ligand and the target molecules. Showing the 3D structures will localize the fitted ligands on proteins and the possible hydrogen bonds formed will be defined. The data obtained were compared to an active compound lenalidomide®, found in the market, as an anti-angiogenic factor.

2. Material and Methods

Molecular docking studies were performed on SwissDock web server using EADock DSS

algorithm [12]. High resolution crystal structures of VEGFR-2 (PDB ID: 2XIR) and COX-2 (PDB ID:1CX2) were obtained from protein data bank. The GaussView 5.0.9 program was used to visualize the optimized geometries of the ligands [13]. All graphical data obtained from the molecular docking studies were visualized using UCSF Chimera software [14].

3. Results and Discussions

Previously synthesized three ligands were studied for molecular docking properties. The three ligands share a common structural similarity of having a backbone composed of a biphenyl, a keto and an oxime group as shown in Figure 1. This study based on the determination of the effects of functional amine groups attached to identical structures for comparison of their docking behaviors. The design of the ligands primarily based on the conformational stability of the overall molecule and reactivity of the functional groups. In order to start molecular docking, candidate molecules were optimized by molecular mechanics for reaching the minimal energy levels. The 3D structures of the target proteins were checked and removed for unwanted groups like water molecules and co-crystallized structures which may interfere with docking. Than Gastegier charges were assigned and polar hydrogens were added as in a routine preparation process. Table 1 shows the overall data obtained from molecular docking studies. All three ligands bonded to the targets spontaneously. Binding energies of Ligands 1, 2 and 3 with VEGFR-2 were Ligand 1 > Ligand 2 > Ligand 3 > lenalidomide® from higher to lower, respectively (with omitted minus sign). All ligands showed a higher binding energy (ΔG) compared to commercial agent. Ligand 1 and lenalidomide® formed a hydrogen bond while Ligand 2 and 3 formed 2 hydrogen bonds with the target which suits with the binding energies. Another important parameter for molecular docking is the full fitness score for ligand-VEGFR-2 couples studied. Obtained fitness scores were directly proportional with the ΔG values of the couples. In addition to the binding energies, total energy of the formed ligand- protein couples indicates the stability of the formed molecule. Lenalidomide®-VEGFR-2 couple formed the most stable molecule with the lowest molecular energy. Secondly, the Ligand 1 and both proteins had four times the lowest molecular energy compared to other ligands. Therefore, the stability of the ligand- protein couples from the most stable to the least were like lenalidomide® > Ligand 1 > Ligand 2 > Ligand 3. As can be seen from the space-filled views in Figure 2; Ligand 1 fits the

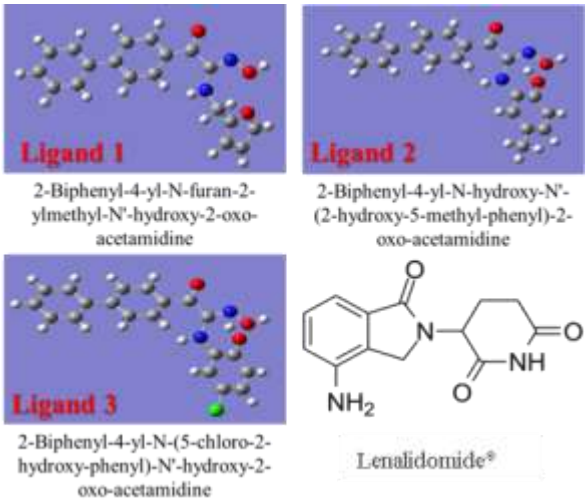

Figure 1. *Optimized structures of Ligands 1, 2, 3 and lenalidomide®.*

VEGFR-2 protein with a higher proximity and orientation, which is in accordance with the full-fitness score, ΔG value and total energy of the Ligand 1-protein couple. In the larger views of ribbon graphics of three ligands (second row from the left) formed H bonds (in orange color) also can be seen which is one for Ligand 1 and two for Ligand 2 and 3. In Figure 3 Ligand 1, 2, 3- COX-2 complexes can be seen. One H bond was formed between the Ligand 1, 2 and COX-2 while two H bonds were formed between Ligand 3 and COX-2. The H bonds contribute a lot to the stability of proteins and other macromolecules, but there seems no correlation between the fitness scores, ΔG values, energy of the couples and the number of H bonds for this study. Proximity may be the determining factor which is directly depended on the 3D shape of the ligand and the protein site it was plugged in. Ligand 2 and 3 are structurally similar only differing in Cl on phenyl group of Ligand 2 was replaced by a methyl group in Ligand 3 while the Ligand 1 bears a furan group attached to the amine group. Three ligands are similar in structure bearing a biphenyl, a carbonyl, an oxime and the amine group. The similarities are strongly correlated to the energy data obtained. Ligand 2 and 3 have closer total energy (39.51 and 38.81 kcal/mol, respectively) compared to Ligand 1 (10.59 kcal/mol) which carries a furan group attached to amine while others carry a phenyl group. The phenyl and furan replacement after the amine group causes a big difference in the energy of the Ligands 2 and 3 which was about four times higher than the energy of Ligand 1. It is also the same for VEGFR-2 and ligand couples. The H bonds were formed between the same amino acids and the functional groups (Arg 44-N-H and Glu 465-C=O) of COX-2 with the same functional groups (C=O and Oxime-H) of the three ligands which accurately

Table 1. *Molecular docking numerical data of Ligands 1, 2, 3 with VEGFR-2 and COX-2*

Target protein	Ligand	ΔG (kcal/mol)	Full fitness score (kcal/mol)	Energy (kcal/mol)	H-bond location (Target&Ligand)	H-bond length (Å)
VEGFR-2 (2XIR)	**Ligand 1**	-8.33	-1573.17	10.27	Asp 174-N-H & Furan-O	2.48
	Ligand 2	-8.20	-1544.39	44.92	Asp 174-C=O & -NH	1.97
					Arg 155-NH & C=O	2.26
	Ligand 3	-7.70	-1537.76	47.29	Asp 174-C=O & Phenyl-OH	2.07
					Arg 155-NH & C=O	1.98
	Lenalidomide®	-7.02	-1629.29	3.43	Serine 154-C=O & Isoindole-NH	2.13
COX-2 (1CX2)	**Ligand 1**	-9.10	-2387.39	10.59	Arg 44-N-H & C=O	2.03
	Ligand 2	-9.62	-2360.63	39.51	Glu 465-C=O & Oxime-H	1.90
	Ligand 3	-9.22	-2359.39	38.81	Arg 44-N-H & C=O	2.49
					Glu 465-C=O & Oxime-H	1.83

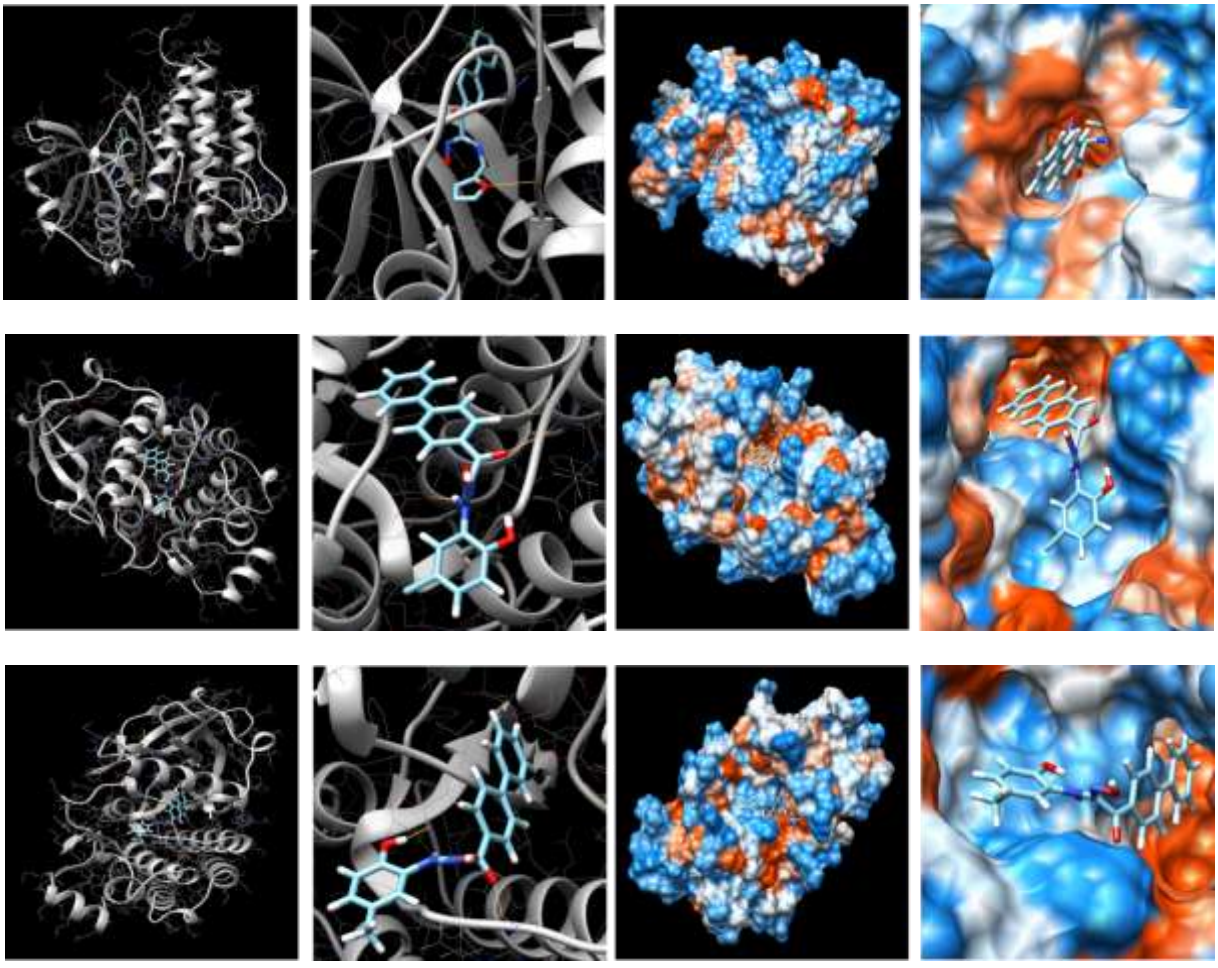

Figure 2. *Ligand 1, 2, 3-VEGFR-2 complexes (from top to bottom). Ribbon (left) and space filled (right) demonstration with closer views.*

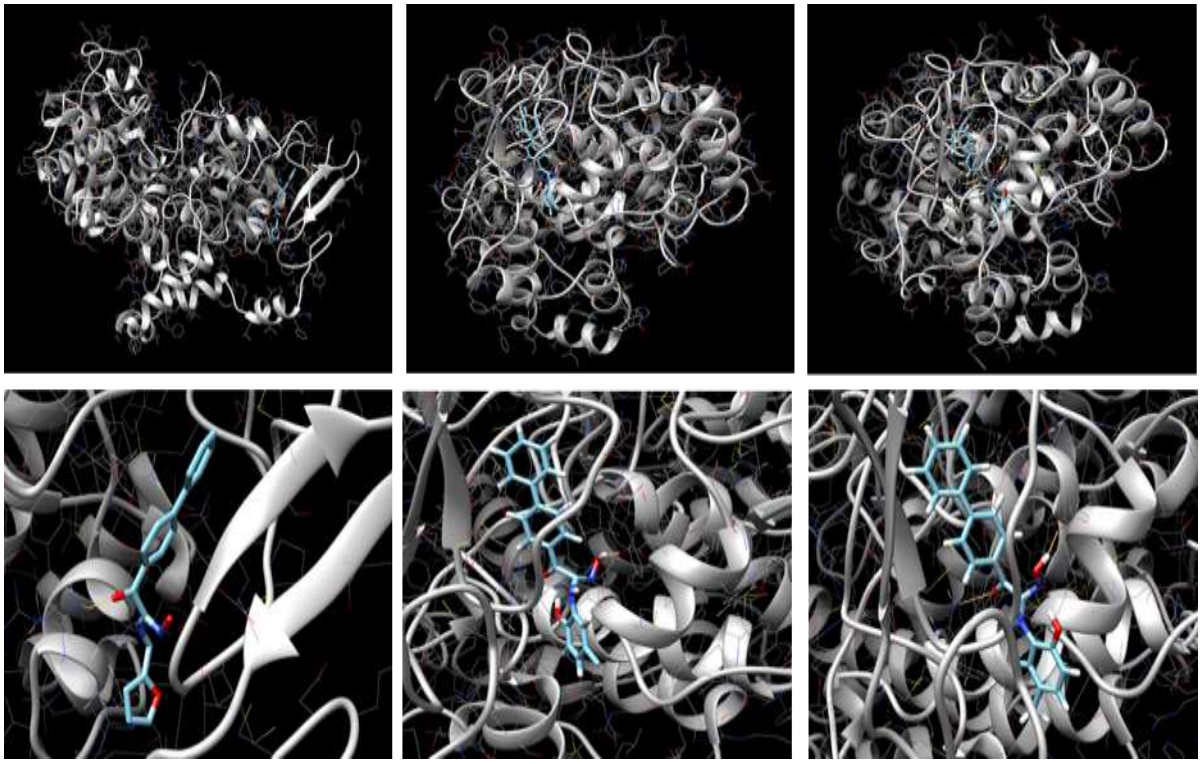

Figure 3. *Molecular docking visuals of complexes of Ligand 1, 2, 3 with (COX-2) enzyme (from left to right) with closer views just below.*

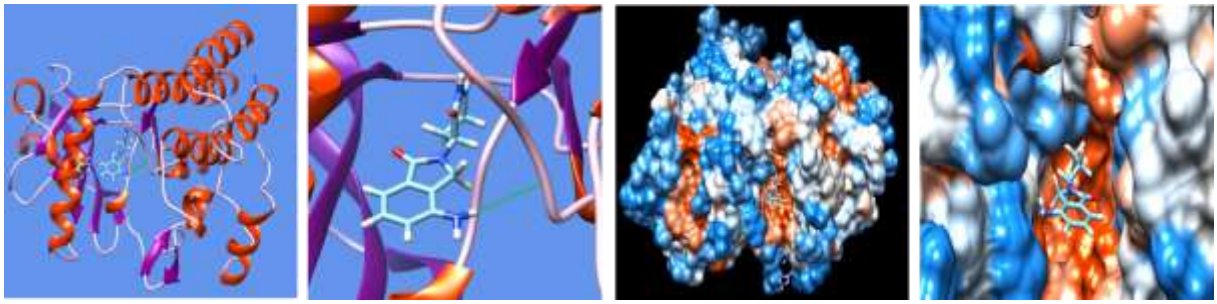

Figure 4. *Lenalidomide®-2XIR complex. Ribbon (left) and space filled (right) demonstration with closer looks.*

indicates that these three ligands were docked to the same site in COX-2. This is also valid for VEGFR-2 ligand complexes. Lenalidomide®-2XIR interactions can be seen in Figure 4. The ribbon shape demonstration shows the location of H bond while the space-filled figures shows the placement of the active ligand to the groove on the 2XIR protein. Potentiality of the three ligands were compared with the active drug lenalidomide® by molecular docking study which is a good indicator for a candidate molecule.

4. Conclusion

Comparison of the commercial product lenalidomide® with the three ligand by molecular docking data provide us information about the interaction status of our molecules with the target proteins. The ΔG values and fitness scores are close while the energy of lenalidomide® is much lower (3.43 kcal/mol) than the proposed ligands (10.27, 44.92 and 47.29 kcal/mol, respectively). It is about three times lower than the Ligand 1 and about 13 times lower than Ligand 2 and 3. This shows us that the commercial product is much more stable than the Ligand 1, 2 and 3. Stability is an important factor for a binding molecule which supposed to inhibit the target protein. However, the other indicators like ΔG and fitness scores are also important for the potentiality of the ligand synthesized. In this study, the Ligand 1 has the closest data to lenalidomide® which may be evaluated as a potential agent. For various reasons, new agents have been synthesized, characterized and tested for their binding behaviors. As a further research, these three ligands may be evaluated and processed for phase studies.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
- **Acknowledgement:** The authors declare that they have nobody or no-company to acknowledge.
- **Author contributions:** The authors declare that they have equal right on this paper.
- **Funding information:** The authors declare that there is no funding to be acknowledged.
- **Data availability statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

[1] Kenakin, T. (2018). A Pharmacology Primer: Techniques for More Effective and Strategic Drug Discovery, 4th ed. *San Diego, CA, Academic Press*,

[2] Strømgaard K, Krogsgaard-Larsen P, Madsen U, (2017). Eds. *Textbook of Drug Design and Discovery*. *CRC Press*;

[3] Gorgulu, G., Cicek, M. B., Dede, B. (2018). Novel Aminoketooxime Ligand and Its Cu(II) and Mn(II) Complexes: Synthesis, Characterization and Molecular Docking Studies. *Acta Physica Polonica A*, 133(2); 250–255. DOI: 10.12693/APhysPolA.133.250

[4] Sliwoski, G., Kothiwale, S., Meiler, J., Lowe, E. W. (2014). Computational methods in drug discovery. *Pharmacological Reviews*, 66(1); 334-395. DOI:10.1124/pr.112.007336

[5] Tammela, T., Enholm, B., Alitalo, K., Paavonen, K. (2005). The biology of vascular endothelial growth factors, *Cardiovascular Research*, 65(3);550–563. DOI:10.1016/j.cardiores.2004.12.002

[6] Wilkinson-Berka, J. L. (2004). Vasoactive factors and diabetic retinopathy: vascular endothelial growth factor, cycoloxygenase-2 and nitric oxide. *Current Pharmaceutical Design*, *10*(27); 3331-3348. DOI:10.2174/1381612043383142

[7] Tuccillo, C., Romano, M., Troiani, T., Martinelli, E., Morgillo, F., De Vita, F., Bianco, R., Gabriella, F., Bianco, R.A., Tortora, G., Ciardiello, F. (2005). Antitumor activity of ZD6474, a vascular endothelial growth factor-2 and epidermal growth factor receptor small molecule tyrosine kinase inhibitor, in combination with SC-236, a cyclooxygenase-2 inhibitor. *Clinical Cancer Research*, *11*(3); 1268-1276. DOI: 10.1158/1078-0432.1268.11.3

[8] Ferrara, N., Gerber, H.P., LeCouter, J. (2003). The biology of VEGF and its receptors, *Nature Medicine*, 9(6); 669-676. DOI:10.1038/nm0603-669

[9] Karipcin, F., Arabali, F., Karatas, I. (2006). Synthesis and characterization of 4-(alkylaminoisonitrosoacetyl) biphenyls and their complexes. *Russian Journal of Coordination Chemistry*, *32*(2); 109-115. DOI:10.1134/S1070328406020059

[10] Karipcin, F., Dede, B., Cengiz, M. (2010). Synthesis of (2-hydroxo-5-chlorophenylaminoisonitroso acetyl) phenyl ligands and their complexes: Spectral, thermal and solvent-extraction studies. *Russian Journal of Inorganic Chemistry*, *55*(4); 530-540. DOI:10.1134/S0036023610040078

[11] Dede, B., Karipcin, F., Arabalı, F., Cengiz, M. (2010). Synthesis, structure, and solvent-extraction properties of tridentate oxime ligands and their cobalt (II), nickel (II), copper (II), zinc (II) complexes. *Chemical Papers*, 64(1); 25-33. DOI: 10.2478/s11696-009-0095-6

[12] Grosdidier, A., Vincent Z., Olivier M. (2011). Swissdock, A Protein-Small Molecule Docking Web Service Based on EADock DSS. *Nucleic Acids Res*, 39(2); 270-277. DOI: 10.1093/nar/gkr366

[13] GaussView, Revision 5.0.9, R. Dennington, T. A. Keith, J. M. Millam, Semichem Inc., *Shawnee Mission, KS, 2009.*

[14] Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., Ferrin, T. E. (2004). UCSF Chimera-a visualization system for exploratory research and analysis. *Journal of Computational Chemistry*, 25(13); 1605-1612. DOI: 10.1002/jcc.20084