Ligand and Structure Based Insilico Studies to Identify VEGFR-2 Inhibitors as Potential Anticancer Agents

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ABSTRACT

Cancer is defined as abnormal cell growth and division that has the potential to infiltrate or spread to other parts of the body. Vascular endothelial growth factor receptor-2 (VEGFR-2) plays a crucial role in many types of cancer. VEGFR-2 is an angiogenesis regulating component that is involved in a variety of disorders and is also required for solid tumor development. The current work seeks to understand the binding mechanism of existing VEGFR-2 tyrosine kinase inhibitors in order to build innovative and effective VEGFR-2 inhibitors. For this investigation, a database of 100 compounds collected from thirteen journals was generated.Using the MOE (molecular operating environment) tool, the co-crystallized structure of VEGFR-2 (2XIR) was utilized to develop a Ligand-based Pharmacophore model. The model has eight features, two of which have been classified as important, and it has been confirmed using the Guner Henry approach. The ZINC database was utilized to screen pharmacophore models, yielding 340 hits that were then used in molecular docking investigations. The top 200 ranking compounds' binding interactions were discovered after docking based on a high docking score.Based on the high docking score, ten drugs with important interactions were identified as new and powerful VEGFR-2 inhibitors for cancer therapy.

Keywords: Cancer, Molecular docking, Pharmacophore, VEGFR-2, Virtual screening.

INTRODUCTION

Cancer is a term that is commonly used to describe abnormal cell growth and division. Some cancers encourage fast cell division, whereas others induce cells to move and divide more slowly. When old cells die in cancer, the dead cells survive and form a tumor-like growth or mass.

Angiogenesis is a complex and well-organized process required for aberrant growth and metastasis. Several growth factors and cytokines that permit and sustain angiogenesis during cancer have been found in recent years, with vascular endothelial growth factor being the most dominating. (VEGFR-2) Li et al. (2014) Blood arteries proliferate in solid tumors in order to give appropriate oxygen and food reserves to malignant cells throughout the metastasis stage (Aziz et al., 2016). The vascular endothelial growth factor (VEGF) and its receptors (VEGFR) have been shown to be potent angiogenesis inhibitors (Plate et al., 1992). VEGF stimulates VEGFRs 1–3 by attaching to the extracellular domain of VEGFR and boosting downstream signaling cascades (2016). (Aziz et al.). VEGFR-2 (KDR) regulates endothelial cell proliferation and transition (Hosen et al., 2017). When VEGF-A binds to the receptor's carboxy-terminal tyrosine residues, cell signaling, vasculogenesis, and angiogenesis are initiated. The active expression of VEGFR-2 promotes downstream cell survival pathways, making it a good candidate for the development of innovative anti-cancer medicines.It is possible to halt tumor growth and angiogenesis by blocking VEGFR-2. As a result, a number of small compounds with VEGFR tyrosine kinase inhibitory properties have been created. Some have been studied as effective antagonists, while others are currently being studied in clinical trials for a range of angiogenic disorders.

OBJECTIVES

1. To find out the binding mode of known VEGFR-2 tyrosine kinase inhibitors
2. To design new and potent inhibitors for VEGFR-2 tyrosine kinase

METHODOLOGY

A database of 100 compounds collected from thirteen articles was created for this study. The co-crystallized structure of VEGFR-2 (2XIR) was then used to build a Ligand-based Pharmacophore modelusing the MOE (molecular operating environment) program. The model consists of eight features, two features were designated as essential and the model was verified using the Guner Henry method. The Guner Henry score was calculated to be 0.93 respectively.

Table 1. Different parameters determined using Guner Henry Score.

S. No	Parameters	Values
1.	Total molecules in database (D)	100
2.	TotalNo of actives in database (A)	35
3.	Hit molecules from the database (Ht)	18
4.	Active Hits (Ha)	15
5.	% Yield of actives (Ha/Ht)	83
6.	% Ratio of actives [(Ha/A) × 100]	42.8
7.	Enrichment	2.38
8.	factor(EF)	20
9.	False negatives (A-Ha)	3
10.	False positives (Ht-Ha)	0.93
	Goodness of fit score (GF)	

Virtual screening was used to identify potential anti-cancer medicines with complicated architecture. So the ZINC database was used to screen pharmacophore models, and 340 hits were discovered, which were then used in molecular docking investigations. The binding interactions of the top 200 ranking compounds were discovered after docking based on a high docking score.

RESULTS

As a result, 10 compounds out of the top 200 compounds exhibited significant interactions with essential residues in the target protein.So, these 10 compounds were chosen as novel and effective VEGFR-2 inhibitors for cancer therapy based on a high docking score.

Table 2. Zinc ID and drug like hit compound properties.

S.No	ZINC ID	Drug like properties	Docking Score
1	ZINC05947311	Mol W:306.33g/mol, logP:2.16,Don:1,Acc:4	-8.2909
2	ZINC06582958	Mol W:311.34g/mol, logP:0.56, Don: 2, Acc: 4	-8.0466
3	ZINC06582958	Mol W:311.34g/mol, logP: 0.56, Don: 2, Acc: 4	-8.0381
4	ZINC06582958	Mol W:311.34g/mol, logP: 0.56, Don: 2, Acc: 4	-8.0360
5	ZINC06582958	Mol W: 311.34g/mol, logP: 0.56, Don:2, Acc: 4	-7.9808
6	ZINC13132446	Mol W:310.34g/mol, logP :0.78, Don:2, Acc: 4	-7.9392
7	ZINC06294454	Mol W:283.33g/mol,logP:2.77,Don:1,Acc:2	-7.9061
8	ZINC32592909	Mol W:267.29g/mol, logP: 1.31, Don:1, Acc: 4	-7.8936
9	ZINC36621466	Mol W:289.27g/mol, logP:1.22, Don:2, Acc: 4	-7..8846
10	ZINC36621466	Mol W: 289.27g/mol, logP:1.22, Don:2, Acc:4	-7.7846
11	Reference	Mol W:464.54g/mol, logP:0.13, Don: 3, Acc: 5	-6.7339

CONCLUSION

Our recent findings described that on the basis of molecular docking experiments, a novel VEGFR- 2 scaffold was created. Finally, 10 compounds were chosen as new and powerful VEGFR-2 inhibitors based on a good docking score. Such potent compounds should be exploited and explored further as prospective guidelines for the creation of new VEGFR-2 inhibitors. Such competitors with amazing processes are likely to advance as new beginning points in the creation of innovative and potent vascular endothelial growth factor-2 receptors as inhibitors of angiogenesis.

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