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Use of Molecular Docking Study to Find Inhibitors Against the Human VEGFR Protein to Treat Hepatocellular Carcinoma

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Abstract: Molecular docking study and computational analysis is applied to all the ligands and outcome of the analysis has been recorded. One molecule (CID11167602) with the potential to become an antiviral medication for HCC (Hepatocellular Carcinoma) is chosen after a virtual screening of significantly 10 chemicals against the 3HNG energy minimized protein structure of VEGF of HCC. Binding energies (-12.5 Kcal/mol) is discovered. Along with ADME, the physiological and bioactivity parameters are accurately anticipated. This chemical's significant binding affinities to the receptor cavity are in line with the results of the docking studies. Furthermore, it is anticipated that the discovered inhibitor will make a better starting point for additional experimental research in the search for anticancer drugs.

Keywords: Hepatocellular carcinoma, VEGFR, Inhibitors, Molecular docking

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Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults and is currently the most common cause of death in people with cirrhosis. HCC is the third leading cause of cancer-related deaths worldwide. It occurs in the setting of chronic liver inflammation, and is most closely linked to chronic viral hepatitis infection (Hepatitis B or C) or exposure to toxins such as alcohol, aflatoxin, or pyrrolizidine alkaloids (Llovet *et al.*, 2018). Certain diseases, such as hemochromatosis and alpha 1-antitrypsin deficiency, markedly increase the risk of developing HCC (Anstee *et al.*, 2019). Metabolic syndrome and NASH (non-alcoholic steato-hepatitis) are also increasingly recognized as risk factors for HCC. As with any cancer, the treatment and prognosis of HCC vary depending on the specifics of tumor histology, size, how far the

cancer has spread, and overall health. The growth of cancers and development of metastasis depend on angiogenesis, that is the adequate structure for blood supply (Finn *et al.*, 2020; Sarkar, 2021, 2022). The process of angiogenesis begins with local degeneration of the basement membrane near capillaries. Then by the invasion of the nearby stroma by the primary endothelial cells in the direction of angiogenic stimuli. Endothelial cells migration is followed by the increase of endothelial cells, organized into 3D structures joining with new analogus structures forming a system of a new blood vessels (Sarkar and Ganguly, 2022). VEGF (Vascular Endotheial Growth Factor) is the most relevant factor for maintaining tumor cells growth and mediates its activity by specific receptors, called VEGF receptors. VEGF is a signalling protein that promotes the growth of new blood vessels. The primary angiogenic receptors for VEGF is VEGFR 1 and VEGFR 2. They are expressed in some types of vascular endothelial and cancer cells. They are the part of tyrosine kinase receptors family (Sarkar and Maiti, 2023). Angiogenesis inhibitors have become an important therapeutic approach in the treatment of hepatocellular carcinoma patients. The main therapeutic inhibition of angiogenesis by sorafenib is increasing overall survival of patients with HCC which is a fundamental element of the treatment of this disease. Other than sorafenib many different inhibitor drugs can treat HCC. The binding mode of different inhibitors with VEGF was computed. Molecular docking studies have been performed (Sarkar *et al.*, 2022). Here my approach is "Blind docking" which start from the beginning without any prior knowledge of the target protein. However, it is a time-consuming method which need several runs and trials. For successful docking performance it needs to have two pillars –a method to explore the ligand-receptor conformation space and a method to relatively order the scoring function. In this study, we focused on structure-based computational modelling of ligand-receptor interactions. The current study looks at various inhibitors (drugs) against 3HNG VEGF (Ferrara, 2004; Tseng *et al.*, 2008).

Materials and Methods

Selection and Preparation of Protein

The amino acid sequence of VEGF protein (3HNG) has been obtained from NCBI. The sequence is entered in the official website of PDB sum to get the detailed analysis of the protein (like how many chains the protein has, if any kind of ligand is bound with the protein, if so then with which chain of the protein it is interacting, binding of water molecules and metals etc.) (http://www.ebi.ac.uk/thornton-srv/databases/pdbsum/). The PDB code of the protein is then put in the official website of the RCSB PDB to get the PDB file of the protein (https://www.rcsb.org/). The HATEM and CONNECTs (metals and water molecules) are deleted from the PDB format of the protein. The protein is then energy minimized using the SPDBV software (Swiss PDB Viewer) (https://spdbv.unil.ch/).

Selection of Ligand Molecules

The selection of the ligands molecule was done from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the 2D structure format was downloaded in SDF format. Then the ADME prediction of all selected ligands have been done from SWISS ADME (http://www.swissadme.ch/) to get all filtered drugs based on Lipinski rule of five. Table 1 illustrates the compound IUPAC name, PubChem ID, and Molecular formula.

Molecular docking study and Visualization

Molecular docking analysis is performed with target like VEGF protein (3HNG) by using CB dock auto blind docking tool. This tool uses Auto Dock for docking purposes. Here first energy minimized protein structure and then one by one all selected bioactive compounds (ligand) are uploaded. Finally docking is started and approximately ten simulations are performed for each simulation, producing docked structures. The least energy configurations are deemed to be the highest binding conformations as a result of this.

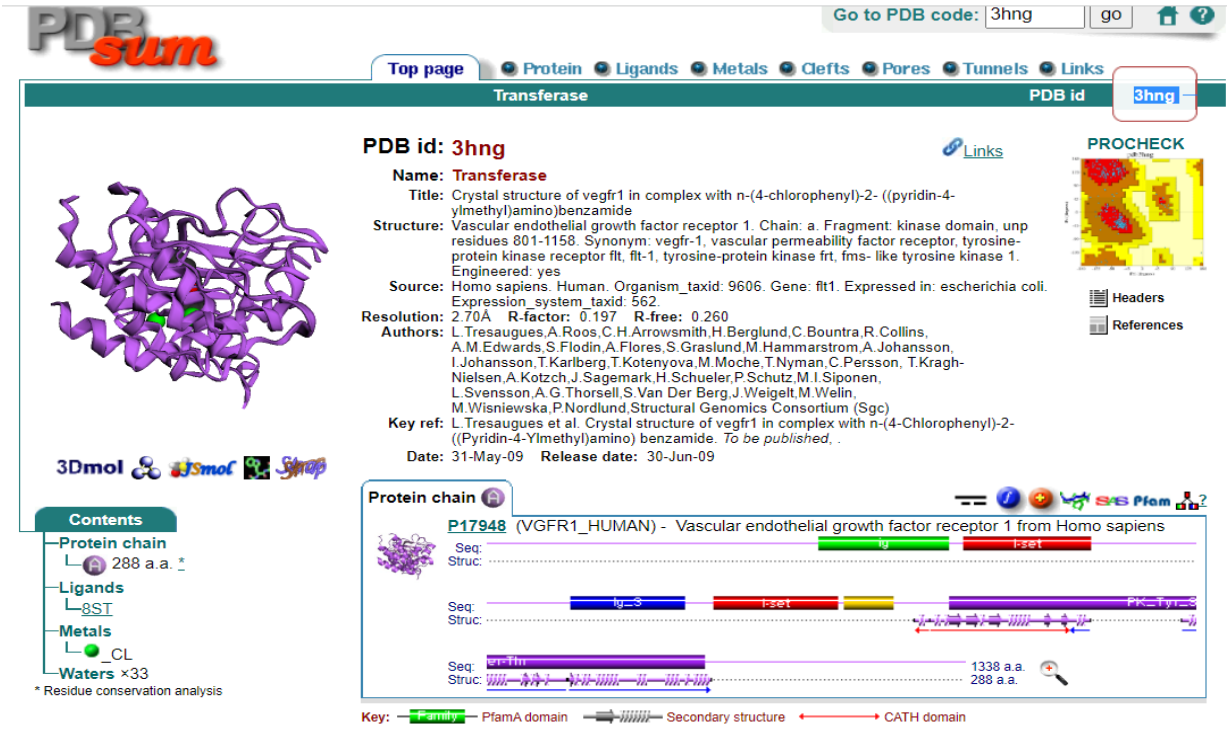

Fig. 1: Structural analysis of the VEGF 3HNG protein (http://www.ebi.ac.uk/thorntonsrv/databases/pdbsum/).

Intra-molecular associations including hydrogen bonds, van der Waals contacts, plus hydrophobic correlations with such an individual bioactive molecule have really been clearly examined using PLIP (Protein-Ligand Interaction Profiler).

Results and Discussion

Table 1 listed all the drugs (ligands) used to investigate the molecular origin of these substances by SWISS ADME. The BOILED-Egg image gives the detailed analysis regarding gastrointestinal absorption (HIA) and blood-brain penetration (BBB) in the function of the position of the molecules (Fig. 2). The white region tells us about the chances of passive absorption by GI tract, and the yellow portion tells us about the high chances for brain penetration. The yolk and white areas are not mutually exclusive.

We used PLIP (Protein Ligand Interaction Proflier) to determine the interacting molecules, energy and as well as the number of hydrogen bonds involved in the '3HNG' protein ligand docking interaction (Table 3; Figs. 4-13).

Docking is the Method which can be used to predict the preferred orientation of one molecule to another molecule when they are bound together to form a stable complex by computational strategies or tools. Modelling the interaction of a drug with its receptor is a complex problem (Zhang *et al.*, 2012; Meng *et al.*, 2014). Many forces are involved in the intermolecular association: hydrophobic, dispersion, or Van der Waals, hydrogen bonding, and electrostatic. The major force for binding appears to be hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions (Liu *et al.*, 2014). Modelling the intermolecular interactions in a ligand-protein complex is difficult because there are so many degrees of freedom and insufficient knowledge of the effect of solvent on the binding association (Ferrara, 2004). The process of docking a ligand to a binding site tries to mimic the natural course of interaction of the ligand and

Table 1: Details of selected ligands

S. No.	PubChem ID	INHIBITOR NAME	Molecular formula
1.	9826472	Sorafenib n oxide	$C_{21}H_{16}ClF_3N_4O_4$
2.	11167602	Regorafenib	$C_{21}H_{15}ClF_4N_4O_3$
3.	9823820	Lenvatinib	$C_{21}H_{19}ClN_4O_4$
4.	25031915	Lucitanib	$C_{26}H_{25}N_3O_4$
5.	49779393	Chiauranib	$C_{27}H_{21}N_3O_3$
6.	71621331	Futibatinib	$C_{22}H_{22}N_6O_3$
7.	86705695	Pemigatinib	$C_{24}H_{27}F_2N_5O_4$
8.	25127713	Poziotinib	$C_{23}H_{21}Cl_2FN_4O_3$
9.	10458325	Tesevatinib	$C_{24}H_{25}Cl_2FN_4O_2$
10.	11234052	Brivanib	$C_{19}H_{19}FN_4O_3$

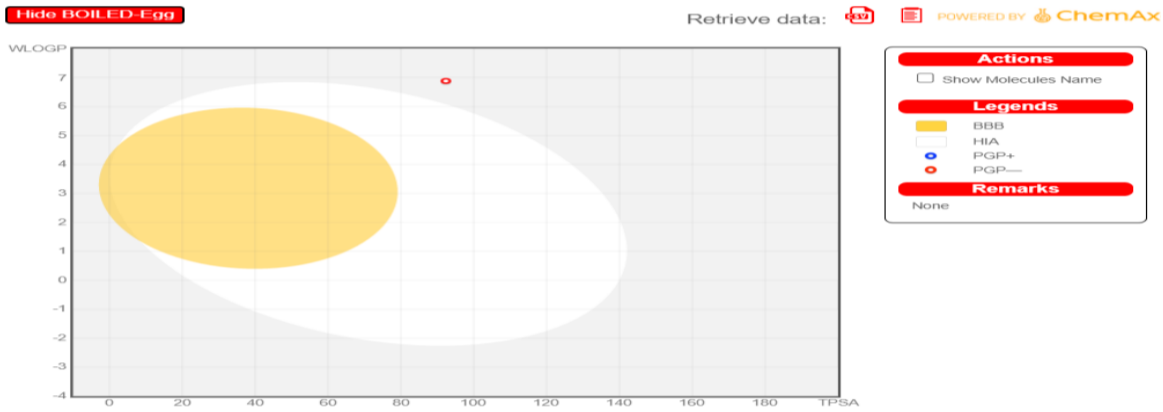

Fig. 2: "BOILED-Egg" image analysis of the ligand PubChem D:11167602; Where BBB stands for, Blood Brain Barrier, HIA stands for, Gastro-intestinal absorption, PGP+ stands for Molecules to be merged to CNS, PGP- stands for Not going to be merged to CNS.

Table 2: ADME predictions analysis of all used drug molecule based on Lipinski rule of five

S. No.	PubChem ID	Molecular Weight (g/mol)	No. of Hydrogen bond donor	No. of Hydrogen bond acceptor	log $p_{o/w}$	Log S [ESOL]	Lipinski Rule violation
1.	9826472	480.82	3	7	1.68	-4.91	0
2.	11167602	482.82	3	8	3.51	-5.27	0
3.	9823820	426.85	3	5	2.68	-4.09	0
4.	25031915	443.49	2	6	3.43	-4.79	0
5.	49779393	435.47	2	4	3.43	-5.93	0
6.	71621331	418.45	1	6	3.09	-3.74	0
7.	86705695	487.50	1	8	3.69	-3.93	0
8.	25127713	491.34	1	6	4.13	-6.16	0
9.	10458325	491.39	1	6	4.37	-6.50	1
10.	11234052	370.38	2	6	3.53	-4.18	0

Table 3: Overview of results for 3HNG energy minimized protein and respective ligand binding with the Binding affinity and Number of residues in interaction as well as Number of hydrogen bond involved in the interaction

S. No.	PubChem ID	Binding affinity (Kcal/mol)	Interaction residues	No. of H bonds	Bonds involved in interaction	Figure Number
1	9826472	-10.5	GLU878, ILE881, LEU882, VAL 909, ARG1021, ASP1040,LYS861	6	Hydrophobic interactions, Hydrogen bonds, pi cation	4
2	11167602	-12.5	LEU833,VAL841, ALA859, GLU878, ASP1040, PHE1041,CYS912,TYR911	8	Hydrogen bonds, Hydrophobic interactions	5
3	9823820	-10.8	LEU833,VAL 841, ALA859, TYR911,ASP1040,PHE1041	7	Hydrophobic interactions, Hyrogen bonds	6
4	25031915	-8.6	GLU878, ILE881, LEU882, ASP1022, TYR1053,GLY1042	4	Hydrogen bonds, Hydrophobic interactions	7
5	49779393	-10.1	ALA874, GLU878,ILE 881, LEU882	1	Hydrophobic interactions, Hydrogen bonds	8
6	71621331	-9.3	GLU878, LEU882, VAL892, HIS1020	2	Hydrophobic interactions, Hydrogen bonds, pi cation interactions	9
7	86705695	-8.1	ALA874, THR 877,ILE 1019, ARG 1021,ASP 1040	3	Hydrophobic interactions, Hydrogen bonds,Salt bridges	10
8	25127713	-10.3	ALA 874, LEU 882, GLU 878, LYS 861, VAL 907	2	Hydrogen bonds, Halogen bonds, Hydrophobic interactions	11
9	10458325	-8.7	ASP 807, GLU 878, ILE 881, LEU 882,LYS 861,VAL907	3	Hydrophobic interactions, Hydrogen bonds,SALT BRIDGES, pi Cation, halogen bonds	12
10	11234052	-8.5	THR877, GLU878, ILE881, LEU 1043,VAL 892	2	Hydrogen bonds,Hydrophobic interactions	13

Fig. 3: Notation guide for the visualization of the interaction between coloured presentation.

its receptor via a lowest energy pathway (Tseng *et al.*, 2008). Molecular docking actually attempts to arrange molecules in favorable configurations by matching complementary features.

We docked 10 inhibitor molecules with target '3HNG' protein (Fig. 5-14). Based on the above results the best docking score is-12.4Kcal/mol (PubChem ID 11167602). Some other ligands have satisfying docking scores. Their docking score are as follows- CID9823820 (-10.8 Kcal/mol), CID 9826472 (-10.5 Kcal/mol), CID 25127713 (-10.3 Kcal/mol) etc. In current hepatocellular carcinoma treatment the most used drug is its receptor via a lowest energy pathway (Tseng *et al.*, 2008).

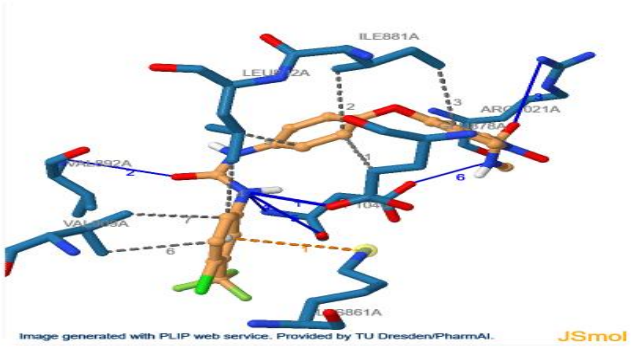

Fig. 4: 3D interaction between 3HNG and sorafenib n oxide.

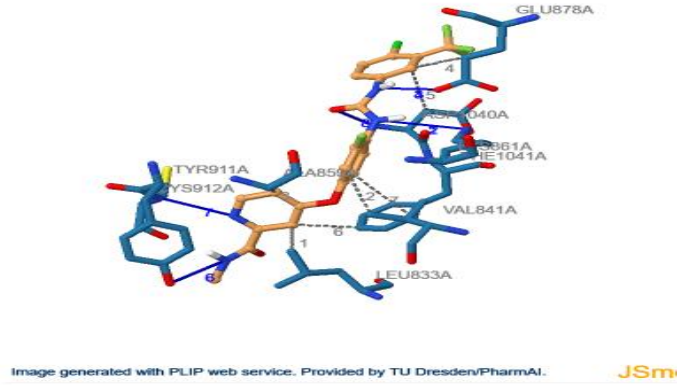

Fig. 5: 3D interaction between 3HNG and Regorafenib

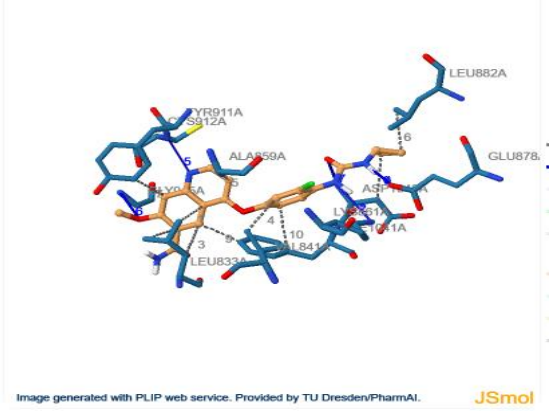

Fig. 6: 3D interaction between 3HNG and Lenvatinib.

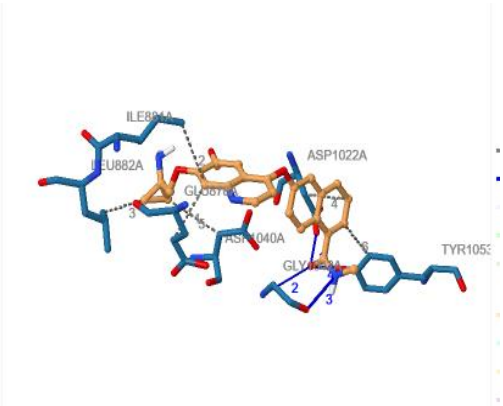

Fig. 7: 3D interaction between 3HNG and lucitanib.

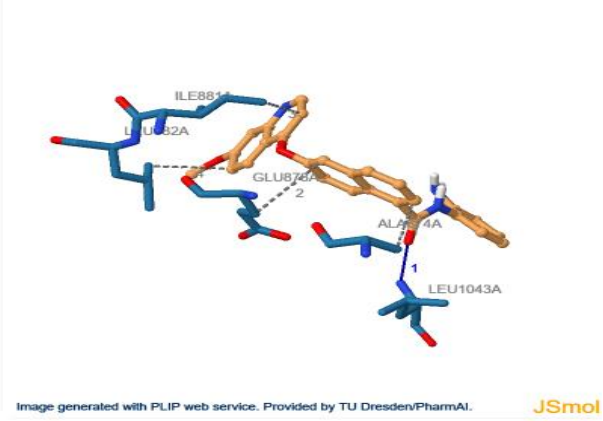

Fig. 8: 3D interaction between 3HNG and Chiaurinab.

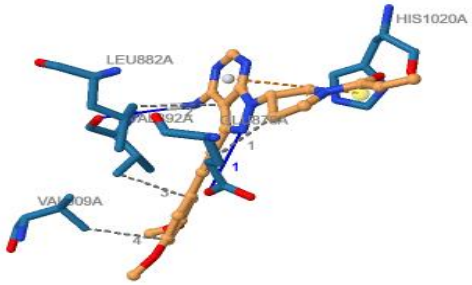

Fig. 9: 3D interaction between 3HNG and Futibatinib.

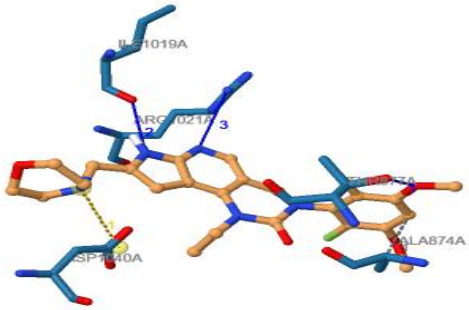

Fig. 10: 3D interaction between 3HNG and pemigatinib.

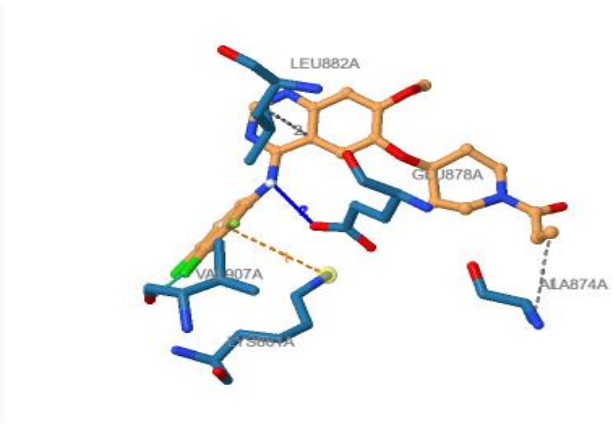

Fig. 11: 3D interaction between 3HNG and Poziotinib.

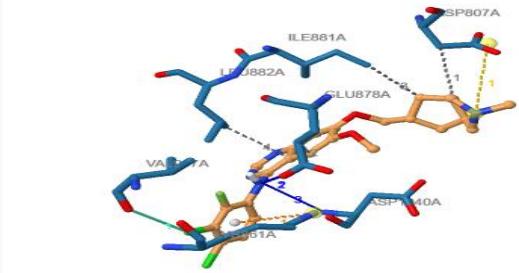

Fig. 12: 3D interaction between 3HNG and Tesevatinib.

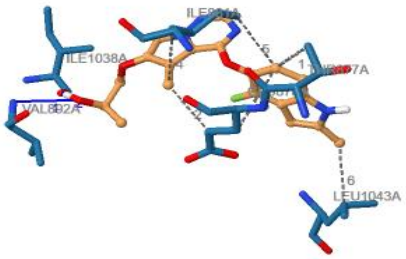

Fig. 13: 3D interaction between 3HNG and Brivanib.

Molecular docking actually attempts to arrange molecules in favorable configurations by matching complementary features.

We docked 10 inhibitor molecules with target '3HNG' protein. Based on the above results the best docking score is -12.4Kcal/mol (PubChem ID 11167602). Some other ligands have satisfying docking scores. Their docking score are as follows- CID9823820 (-10.8Kcal/mol), CID 9826472 (-10.5 Kcal/mol), CID 25127713 (-10.3Kcal/mol) etc. In current hepatocellular carcinoma treatment the most used drug is 'Sorafrnib' (Docking score -10.5 Kcal/mol). But we got another better inhibitor after docking syudt i.e. Rhegorafenib (CID 11167602). We can make further research about this inhibitor's efficiency against hepatocellular carcinoma.

Conclusion

Every ligand is subjected to a computer analysis and molecular docking investigation, with the results documented. Every ligand is subjected to a computer analysis and molecular docking investigation, with the results documented. After

a virtual screening of ten compounds that significantly impacted the 3HNG energy reduced protein structure of VEGF of HCC, one molecule (CID11167602) was selected as a potential antiviral therapy for HCC. It is found that the binding energies are -12.5 Kcal/mol. The physiological and bioactivity characteristics are properly predicted in addition to ADME. The substantial binding affinities of this compound to the receptor cavity are consistent with the findings of the docking experiments. Moreover, it is expected that the identified inhibitor would provide a more robust foundation for future experimental studies aimed at discovering anticancer medications.

Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval not required.

Author Contributions

SD planned this project, written manuscript; *MA* executed entire work. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

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