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Docking Study of Altered Nelfinavir & Indinavir with Protease of Human Immunodeficiency Virus

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ABSTRACT

Nelfinavir and Indinavir are protease inhibitors that function against HIV-1 (HIV-1). Protease inhibitors act by preventing HIV's protease enzyme from functioning. Infectious HIV-1 protease enzyme is proteolytic enzyme in nature that transforms virus causing polyprotein precursors into particular functional proteins. Nelfinavir and Indinavir bind to the protease's active site and prevent it from working. This inhibitor prevents the breaking of virus causing polyproteins, preventing the growth of immature and the non-infectious virus causing particles. However, protease inhibitors are always utilized with at least two further drugs which are anti-HIV drugs. Using the pubchem database from NCBI, we used docking techniques to find the structures of Indinavir and nelfinavir. Then used ds4.1 to modify it then open in auto dock or pay mole to see their attachment after docking with protein.

Keywords: *Nelfinavir, Indinavir, Protease, Docking, Pay mole, Auto dock, DS41, Auto dock vina.*

1. Introduction

Indinavir and Nelfinavir are protease inhibitors that work against HIV-1 (HIV-1). Protease inhibitors act by preventing HIV's protease enzyme from functioning. Infectious HIV-1 protease enzyme is proteolytic enzyme in nature that transforms virus causing polyprotein precursor into particular functional proteins. Indinavir and Nelfinavir bind to the protease's active site and prevent it from functioning. This inhibitor prevents the breaking of viral polyproteins, preventing the development of immature and the non-infectious viral particles. Protease enzyme inhibitors are always used with two other anti-HIV drugs.

Indinavir and Nelfinavir has been used to treat not only AIDS but also Hepatitis C. The hepatitis C virus infects almost 200 million people globally. Cirrhosis, hepatic failure, and hepatocellular carcinoma impact world's population of around 3% and with 3-4 million newly formed infections occurring each year that causes cholangitis, hepatic malfunction, and liver cancer.

Hepatitis virus C is a Flaviviridae pathogen, which means it's an enveloped RNA virus. With at least six genotypes and a variety of subtypes, it is only the component of the Hepaci virus species. There is no effective HCV vaccine, and the only typical treatment is a mixture of pegylated interferon-alpha (IFN-Peg) and virazole, which works with just half of chronically tainted patients.

Molecular docking now has become a crucial part of drug development process. While its inception in the 1980s, improvements in PC hardware, as well as an increase in the number of and simplicity of access to tiny molecule and protein structures, have aided the increase of new methodologies, making docking more admired in both industrial and academic setting. The procedures by which docking has been employed to help various drug development actions have evolved over time. Docking was first formed and utilized as a stand-alone technique, but it is nowadays commonly used in combination with other computational approaches in incorporated workflows.

2. Materials and Methods

Preparation of Data Set

Nelfinavir and Indinavir protease structures were taken from Protein Data Bank. SMILES strings for medication and lead compound, such as CID 5362440 and CID 64143, were retrieved from the pubchem data base. Indinavir and nelfinavir 3D structures were acquired as SDA files from Pubchem.

ADMET

To determine molecular characteristics like membrane absorptivity, polar surface zone, while the other is solubility, fundamental molecular descriptors like logP, TPSA molecular weight (MW), or the number of hydrogen-bond acceptors and contributors in a molecule are always utilized. These molecular characteristics were used to construct the "rule of five." Most compounds with strong membrane permeability and drug likeness have MW five hundred, estimated Octanol–H2O partition coefficient, log P 5, and H-bond donor 5, acceptors ten, according to the rule. As a result, Rule of Lipinski's Five was employed to measure the solubility features of the lead compounds, including metabolism, distribution, adsorption, and eradication called ADME properties. All of the compounds of lead present in this investigation were evaluated using the MOLINSPIRATION tool to determine their molecular properties and bioactivity. Superior lead constructs, that may be drug like than other previously anticipated, are required for successful drug development. Early in the drug development process, toxicity and weak pharmacokinetics should be avoided. As a result, the sensations were more partitioned with the drug-likeliness, poisonousness properties, and drug scoring values. While these physio-chemical parameters for the filtered position of hits were calculated by means of the OSIRIS that is Property Explorer tool.

The OSIRIS algorithm generates a entire list of all existing fragments with related drug-likeliness from a record of about 5,300 different substructure pieces formed by 3,300 traded pharmaceuticals and 15,000 commercially available chemicals. To calculate the compound's drug score values and in general likelihood that succeed to a medicine, the drug score value is a total value that integrates drug-likeliness that include logS, MW, cLogP, and toxicity concerns.

Molecular Docking

The docking method starts with the discovery of a ligand attaching site in a receptor molecule, which is followed by the docking of possible ligands into that site. While the lead related compounds produced from the ligand-dependent VS testing that used in docking calculations and energy of binding evaluation. In molecular docking we used 3d structures of ligand obtained from pubchem id then we modify it by changing its atom with atom of our choice. Then we take protein pdb file which is open by using software **Pay mole or Discovery studio 4**. It opens in discovery studio and removes its inhibitors by choosing select ligand option. Then remove its water molecule and save it as protein data bank file. Then open it in **Auto dock**soft wear where make it grid and remember it x,y,z dimensional and central values which is helpful in docking then save it as pdbqt file. Now open modified ligand in auto dock and save it as pdbqt file also and save it in software folder which install in program files separately and known as **Auto dock vina**. Then making a conf file and put protein pdbqt and ligand pdbqt file after that put x, y,z central and dimension values of grid.

Mediterranean Journal of Basic and Applied Sciences (MJBAS)
Volume 6, Issue 3, Pages 48-54, July-September 2022

Then type the following command to begin the docking procedure: Click the window button with R, then give a space, then click run, then hit cmd, then press enter, then type cd. Enter, then cd..., then enter, then cd space vina, then enter, then write vina(space)—config (space) When you type conf.txt(space)—log(space)log.txt, the docking process will begin, which will take 10 to 15 minutes. The docking result will be saved in a log file, which can be split by using the vina split (space) — input (space) out command, which is added to the end of the docking result. Pdbqt.

3. Results

We take the 3d structures of nelfinavir and indinavir from pubchem database. Comparable structures are thought to have similar functions. The results of docking of nelfinavir modify ligand have larger affinity as compared to unmodified ligand the affinity energy of unmodified ligand has -10kcal /mol while affinity energy of modified nelfinavir ligand has -10.1kcal/mol so modified nelfianvir ligand effectively help to inhibit the growth of protease enzyme which caused HIV and Hepatitis C. While my 2nd ligand have less affinity energy as compared to unmodified ligand the affinity energy of modified ligand is -8.4kcal/mol while unmodified ligand has energy -11.00kcal/mol. It shows that unmodified ligand is most effective to inhibit the production of protease enzyme. I modify the nelfianvir by converting H67 into O67, C14 into H14, O4 into S71.While in indinavir I change H92 into C92, H63 into O63, H87 into N87, H84 into C84.

Table 1. Modifications of different ligands

Ligand Name	R1		R2		R3		R4	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Nelfinavir	H67	O67	C14	H14	04	S71		
Indinavir	H92	C92	H63	O63	H87	N87	H84	C84

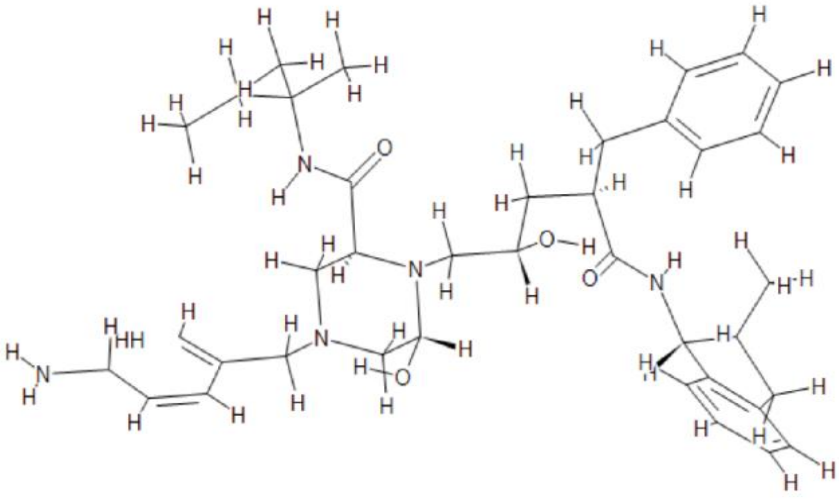

Fig.1. Structure of Indinavir

Mediterranean Journal of Basic and Applied Sciences (MJBAS)
Volume 6, Issue 3, Pages 48-54, July-September 2022

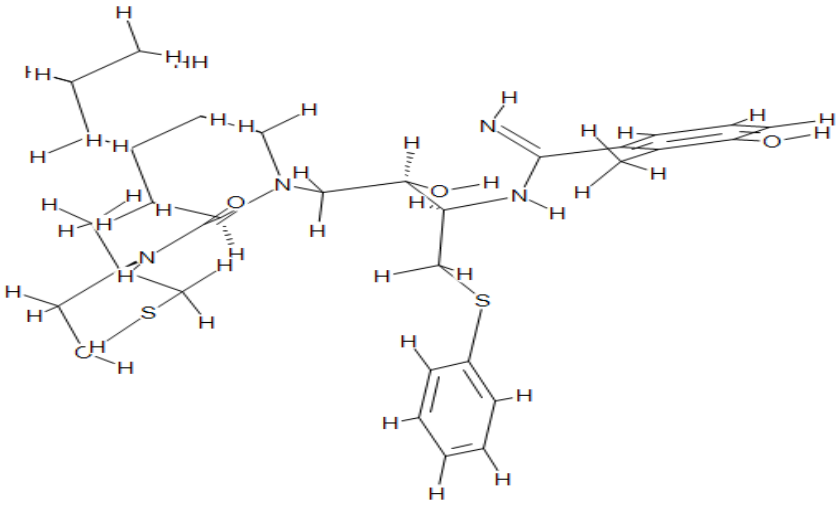

Fig.2. Structure of Nelfinavir

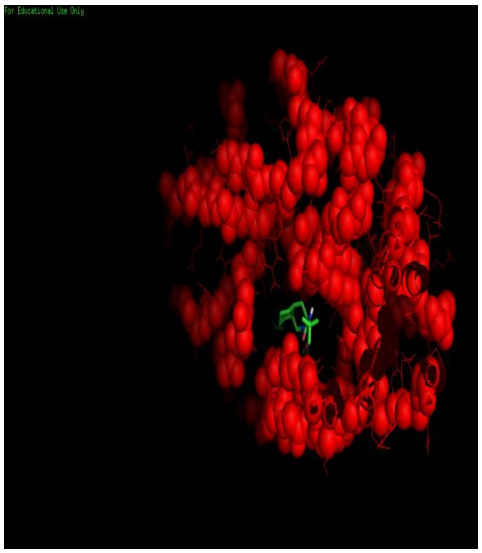

Fig.3. Ligand 1 attachment with protein

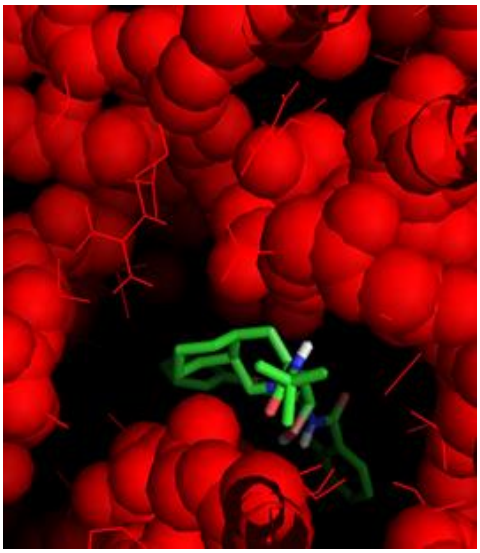

Fig.4. Ligand 2 attachment with protien

Fig.5. Ligand protein attachment

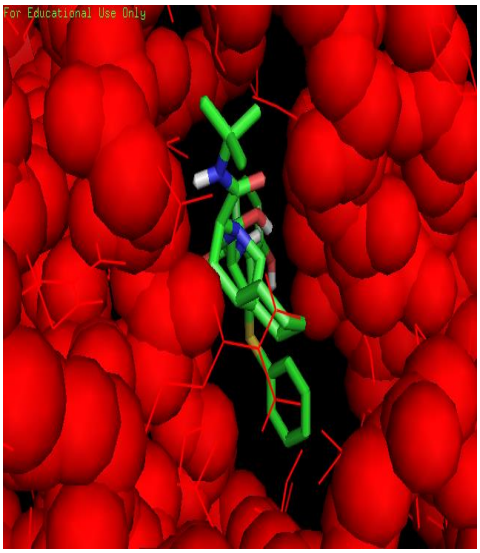

Fig.6. Ligand protein attachment

Docking Results of Ligands With Protein

Table 2. Molecular docking results of ligands with protein

Name	1 (KCAL/ MOL)	2 (KCAL/ MOL)	3 (KCAL/ MOL)	4 (KCAL/ MOL)	5 (KCAL/ MOL)	6 (KCAL/MOL)	7 (KCAL/ MOL)
Unmodified nelfinavir	-10.0	-9.9	-8.4	-8.2	-8.0	-7.9	-7.8
Modified nelfinavir	-10.1	-9.9	-8.7	-8.6	-8.4	-8.2	-8.1
Unmodified nelfinavir	-11.0	-10.5	-8.9	-8.9	-8.7	-8.7	-8.6
Modified Indinavir	-8.4	-8.3	-8.0	-8.0	-7.9	-7.3	-7.2

Ligand's ADMET Properties

Table 3. ADMET properties of ligand compounds

Structure name	MlogP	S+logP	S+logD	Rule of 5	Rule of 5_code	MWT	M_NO	T_PSA	HBDH
Ligand 1	0.891	2.234	2.158	3.000	HB,Mw,NO	672.873	11.000	164.280	7.000
Ligand 2	3.242	4.598	4.571	1.000	Mw	567.796	7.000	101.900	4.000

Scoring of Modify Ligand

Table 4. Modified ligand's scoring

LIGAND NAME	Ligand	Rmsd	Rank (score)	score
Ligand 1	0	None	1	-162
Ligand 2	0	None	1	-76

4. Discussion

The hepatitis C virus infects almost 200 million people globally. Cirrhosis, hepatic failure, and hepatocellular carcinoma impact world's population of around 3% and with 3-4 million newly formed infections occurring each

year that causes cholangitis, hepatic malfunction, and liver cancer. Indinavir and Nelfinavir are protease inhibitors that work against HIV-1 (HIV-1). Protease inhibitors act by preventing HIV's protease enzyme from functioning. Infectious HIV-1 protease enzyme is proteolytic enzyme in nature that transforms virus causing polyprotein precursor into particular functional proteins. Molecular docking now has become a crucial part of drug development process. Docking was first formed and utilized as a stand-alone technique, but it is nowadays commonly used in combination with other computational approaches in incorporated workflows.

Nelfinavir and Indinavir protease structures were taken from Protein Data Bank. SMILES strings for medication and lead compounds were retrieved from the pubchem data base. To determine molecular prospects like membrane absorptivity, polar surface zone, and the other is solubility, fundamental molecular descriptors like logP , TPSA molecular weight (MW), or the number of hydrogen-bond acceptors and contributors in a molecule are always utilized. Comparable structures are thought to have similar functions. The results of docking of nelfinavir modify ligand have larger affinity as compared to unmodified ligand the affinity energy of unmodified ligand has -10kcal /mol while affinity energy of modified nelfinavir ligand has -10.1kcal/mol so modified nelfianvir ligand effectively help to inhibit the growth of protease enzyme which caused HIV and Hepatitis C. Nelfinavir & indinavir are used as drugs but it is not most effective drug against HCV. They have some limitatons. Modify Nelfianvir have more affinity as compared to present nelfinavir inhibitor while modify indinavir have less affinity as compared to present Indinavir.

5. Conclusion

Despite the fact that no particular vaccine is available for HCV disease while the recent standard treatment of Peg-IFN/Ribavirin is related to the various side effects (that are melancholy, nuisance, fever, flu-like indications, hemolytic anaemia), significant progress has been made in the research field and experimental development of innovative antiviral drugs. The most difficult part is developing protease inhibitors which can be taken through mouth, and they have minimal harmfulness and side effects, enhanced SVR, more distorted potency, are pangenotypic, that are affordable. Our research found two lead compounds on structure-based drug design and resemblance searches.Nelfinavir & indinavir are used as drugs but it is not most effective drug against HCV. They have some limitatons. Modify Nelfianvir have more affinity as compared to present nelfinavir inhibitor while modify indinavir have less affinity as compared to present Indinavir.

Declarations

Source of Funding

This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare no competing financial, professional, or personal interests.

Ethical Approval

Ethical approval for this study was obtained from Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University, Multan, Pakistan.

Consent for publication

The authors declare that they consented to the publication of this research work.

Availability of data and material

The authors are willing to share the data and material according to relevant needs.

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