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Identification of Novel Lead to Inhibit HIV Protease: A Computational Approach

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ABSTRACT

Human Immunodeficiency Virus [HIV] attacks the body's immune system and there is currently no effective cure. HIV protease inhibitors prevents the HIV to multiply, interrupting the HIV life cycle. HIV protease inhibitors are widely used for the treatment due to their importance in HIV management, but they can cause potentially serious side effects. For researchers in the field of drug discovery the developing moiety for HIV treatment that is effective and has minimum side effects is a significant problem. The current computational research studies identify novel HIV protease inhibitors with minimal side effects and high efficacy. HIV protease inhibitors were used in generating the hypothesis for pharmacophore modelling using PharmaGist webserver to discover the new entities. Through the ZINCPharmer web server, 1000 most comparable pharmacophoric ligands that are feasible were identified. By the application of Data Warrior tool, the compounds were filtered andused along Autodock Vina for molecular docking. According to the binding affinity and amino acid interaction top ten ligands are subsequently evaluated for ADMET properties using PKCSM webserver. ZINC40825778 compound with binding score and having good interaction with key amino acids of HIV has been identified for further development to treat HIV.

Keywords: *AIDS, HIV protease, Pharmacophore modelling, Molecular docking*

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INTRODUCTION

The immune system is disrupted by the virus known as HIV. The immunodeficiency virus (SIV), a chimpanzee-specific virus, is the root of HIV. After chimpanzees were hunted for food, the blood that carried the infection was likely exposed to by humans. A person can contract HIV, a sexually transmitted illness [STI], by coming into touch with bodily fluids. When a person is exposed to the virus, it may alter their cells, which may then encourage their cells to produce more virus. It weakens the immune system, which makes it simpler for a person to get sick [1].CD4 cells, which are immunological cells, are the target of the human immunodeficiency virus. There are many kinds of Neutrophils, that are either white blood cells which go over the body and search for infections, faults, as abnormalities in all the other cells. To grow, HIV seeks for and infects CD4 cells. The outcome is the destruction of the cells and a reduction in the body's ability to fight against new infections and disorders. As a result, as well as their consequences, opportunistic infections and several types of cancer are more prone to develop. It's crucial to remember that some HIV-positive individuals may go for long stretches of time without exhibiting any symptoms. Even as HIV is a chronic condition, it could potentially be prevented from spreading and from getting worse using a variety of strategies and remedies [2]. HIV stages: HIV-positive people normally go through three distinct phases without treatment. Yet, HIV medicine can slow or stop the advancement of the illness. Because of advancements in HIV medication, the passage of HIV to Level 3 [AIDS] occurs less typically now than it did in the beginning.

Stage 1: Acute HIV disease: people who are highly hazardous and have higher Disease blood levels. Flu-like signs and symptoms exist in many people. If you believe someone could have been tested to Virus and are having flu-like symptoms, get tested.
Stage 2: Chronic Signs and symptoms: Often referred to as therapeutic incubation or asymptomatic HIV infection, this stage is the most advanced. HIV continues to remain alive and still has the power to reproduce within the body. Individuals might not appear sick or have any symptoms throughout that time, but they can potentially transmit HIV. The few who followed the advised HIV care plan cannot ever develop Level 3 [AIDS]. This gap should last about 10 years or longer, or it could pass quite rapidly, without HIV treatment [3]. Towards the end of this stage, due to a rise in HIV infectivity, the individual may enter level 3.
Stage 3-The third stage of AIDS is when Pathogen is most severe. Risks caused by AIDS include high rates of infection and the chance for HIV transmission. Patients with AIDS have significantly damaged immune systems. People are so much more susceptible to contracting illnesses such critical infections. Despite receiving medical, individuals who have AIDS commonly only live for 4 years fewer [4].
Some Disease individuals face no symptoms for up to a year after becoming infected. Although while a somebody with no illness may not be as inclined to seek healthcare, remains a sizable opportunity for transmission. Regular testing is encouraged by experts to make sure everybody is aware of their Infection status. When this is happening, 2-4 weeks after contracting the infection, about two-thirds of patients present flu-like effects. These symptoms are described to as acute retroviral syndrome. Certify of HIV infection may include fever, chills, sweating, enlarged glands or swollen lymph nodes, a broad rash, weakness, and pain, specifically joint ache and body aches, as well as a sore [5]. These symptoms and indications are the result of the immune system's struggle with the sickness. Someone who displays multiple of these symptoms and who could have contracted HIV within the past 2 or weeks of their life needs to get tested.Direct contact with contaminated blood, blood products, or tissues, sexual interaction with infected partners, and perinatal transmission from infected mothers to their offspring are the three main ways that HIV is spread. Although there is a less than 1% chance of contracting HIV through sexual contact, it is believed that 70% to 80% of those with the illness do so globally. Although heterosexual transmission is proportionally more common now than it was in the early years of the pandemic, male-to-male transmission is still the most frequent pattern in the United States [6,7]. HIV transmission potential risks associated with direct blood contact is higher: When infected blood or blood products are transfused, the infection rate might reach 90%. Whole blood, blood cellular components, plasma, and clotting factors can all spread HIV [8,9]. Antiretroviral therapy [ART] is the way of referring to the HIV treatment. As part of ART, a daily Screening and treatment regimen, or collection of HIV drugs, is taken. All HIV-positive people are asked to begin with ART. While ART cannot cure HIV, HIV drugs help those who have the virus live longer, healthier lives. ART reduces the likelihood of HIV transmission here too [10].Protease inhibitors are no longer used as a stand-alone therapy dueto negative effects and increased efficacy in combination therapies. Long-term use of most inhibitors is accompanied by adverse effects, the most notable of which is a condition known as HIV protease inhibitor-induced metabolic syndrome [11,12].
Hence the present study aims to identify novel lead moieties as potent inhibitor of proteases for the treatment of HIV.

MATERIAL AND METHODS

Pharmacophore modelling: Creating a three-dimensional structure called a pharmacophore by sketching out the physiologically powerful chemicals necessary for ligands to bind to and interact with certain target proteins. A pharmacophore is a spatially mutually oriented atom or group of atoms that is thought to interact with and recognise a receptor or the active site of a receptor. Using an open web server called PharmaGist, the compounds were put through pharmacophore modelling[13-15]. An indirect technique for creating pharmacophoric characteristics for a group of compounds is called PharmaGist. Sybyl Mol2 typed components and a verified email address were presented. To create the functional group in mol2 format, the server includes a variety of potential configurations of the components entered [16,17].
Molecular docking: Using ZINC data base, the chemical structure of each ligand was taken. Curated compilation of organic compounds that are offered commercially is ZINC database, which is carefully made for virtual screningand is used by investigators in pharmaceutical companies, research universities and Biotech Company. And the structure of FDA approved drugs was downloaded from Pub Chem.The RCSB Protein Data Bank, a resource for muti structure data of major biological molecules like proteins and nucleic acids, was used to retrieve the usual work begins of the target protein. The standard structure

file from the PDB is unsuitable for use right away in calculations for molecular modelling. A normal PDB form file only contains heavy atoms; however, it may also contain co-crystallized ligands, metal ions, water molecules, and co-factors. As a result, purification use the web-based tool CHARMM-GUI to interactively build complex parts as evaluate their variables. A prepared structure is necessary for Receptor Grid Generation, including all atom structures with the proper bond ordering and formal charges. Favourable contact between one maybe more complex and a receptor molecule, which is often a protein, as determined by AUTODOCK. Following the geometry and capabilities of the receptors, various sets of fields are reproduced on a grid to give progressively more precise assessment of reagent poses [18]. The settings in each tab of the transmitter grid generation interface allow setting up the AUTODOCK constant, defining the receptors organization by rejecting any cross ligand that may be present, and figuring out the location and size of the cell surface when it is represented by receptor grids. Near the receptor's binding site, a grid it was generated. AUTODOCK VINA is used to carry out ligand docking. AUTODOCK VINA having a look for appropriate interaction among a receptor molecule, often a protein, and one or much more ligand molecules. The receptor may include more than one molecule while each ligand acts as a single molecule. A protein and a co-factor.When AUTODOCK VINA was used in inflexible docking mode, domains to every input ligand were generated. In flexible docking, ligand posture is the summation of a ligand's location, orientation, and form with respect to the receptor.The AUTODOCK VINA-generated ligand pose is subjected to several multilayer filters that assess how well the ligand reacts with the receptor. Initial filters evaluate the ligand's spatial fit to the identified active site, and a grid-based approach is used to study the symmetry of ligand receptor interactions[19]. Then its final scoring is done. The target protein the typical structure file was gathered out from RCSB's Protein Data Bank andpurified using CHARM-GU1. Using the program AUTODOCK VINA experiment were performed. Oftotal substrate,by using the protein preparation wizard, complicated lighter coordinates were created for AUTODOCK VINA calculations. A fresh ligand file is created using the P-Prep script, and all residuesaside of those which are reasonably near to the binding neutralised. Finally, the software was allowed to run to start the docking process, where in each ligand was made to bind with the active sitepresent within target sequence under report's active pocket. The pdbqt file which is obtained from the docking is complexed with the protein structure for visualization. In Biovia software, the 2D and 3D structure of the complexes are visualized for studying ligand interactions and enhanced presentation [20].

ADMET studies: After the molecular docking studies, ADMET STUDIES [physicochemical properties] of the ligand was studied such as PKCSM Website after it into smiles by using an online smile translator converting [http://cactus.nci.nih.gov/translate/] and the obtained data was helpful in determining its efficacy and toxicity[21-23].

RESULTS AND DISCUSSION

Ligand based Pharmacophore modelling: Using the PharmaGist server, the pharmacophore theory for HIV protease inhibitors was created. The molecule via PharmaGist consists of one aromatic ring and two hydrogen bond acceptors placed apart by a given distance**.** The result obtained from the PharmaGist is uploaded in the ZINCPharmer, it will screen and recover the compounds having same pharmacophoric features from the ZINC database.The derived pharmacophore model helps to determine the structural need for HIV protease control. screened molecules were uploaded to the DataWarrior,besides that, the molecules are separated in accordance with the physicochemical properties, I.e., the log p value, molecular weight, hydrogen donor, hydrogen acceptor and polar surface area, of the standard HIV protease inhibitors. For molecular docking tests, all these components were supplied as an SDF download file.

Molecular Docking Studies: Molecular docking work on HIV protease inhibitors was made**.**The targeting protein's bioactive pocket has PDB ID: 6xqi was the location of the main strong interactions that could lead to active conformations**.** Determining the linkages between proteins took this process. found in the ZINC database. Utilizing AutoDock Vina, molecular docking investigations were carried out.Indinavir, Saquinavir, Nelfinavir, Lopinavir, Darunavir, Fosamprenavir, Ritonavir and Amprenavir are currently used HIV- protease inhibitors. Among these inhibitors Indinavir docking result of -7.8 kcal/mol was obtained. and as conventional hydrogen bonds utilizingLEU20, GLU24 and Amide Pi-Stacked with LEU39 then Alkyl & Pi- Alkyl interaction with HIS40, LYS27, TRP54, ILE60, LEU42. Hence, the interaction suggested above may be considerable and contribute for the inhibitory features of molecule as HIV-Protease inhibitor.

The chemical was submitted to docking after being acquired as from ZINC database using ZINCPharma depending on the pharmacophore. For docking studies with the target proteins PDB ID: 6xqi, 6 molecules were chosen. To compare compound binding interactions with best docking (mostly negative), the

docking was examined. The hit compound's classification as that of an HIV inhibition may be determined with the use of this comparison. The chemicals are determined based mostly on binding interaction. A docking score of between -5.4 and -9.1 kcal/mol is possible. A molecule named ZINC18196596 has been found by molecular docking to have the high similarity value of -9.1 kcal/mol and to display typical hydrogen bond interactions with HIS40, ASP52, and pi-cation interactions with LYS27 then LEU42, VAL57 with Pi- Alkyl.Using AutoDock tools and the Biovia Discovery Studio Visualizer, binding interactions across docked compounds and the proteins were discovered. The amino acid residues HIS40, ASP52, LYS27, GLY51, LEU39, LEU42, and VAL57 were implicated in the binding interaction. These selected compounds bind to conventional medications in a manner that is consistent with what the molecular docking analysis has shown. These six substances can therefore prohibit the HIV Protease for function**.**The docking results of are shown in the table 1. 2D& 3D structures are shown in fig 1-3.

Table 1: ZINC compounds with its binding affinities

Compound	Docking score	Interacting residues	Type of interactions
ZINC40825778	**-8.4**	LEU39 ASP52 HIS40, ARG36 LYS27 LEU42, VAL57, TYR47, TRP54	Conventional hydrogen bond Carbon hydrogen bond Unfavourable positive-positive, Unfavourable Donar-Donar Pi-Cation Alkyl, Pi-Alkyl
ZINC58881581	**-6.5**	HIS71 ILE63 TRP38, PHE34 LEU67	Conventional hydrogen bond Pi-Sigma Pi-Pi T Shaped Alkyl, Pi-Alkyl
ZINC2036593	**-7.6**	ARG96 HIS40 ASP52, GLY56 GLY51 LEU99 VAL91, VAL57	Unfavourable position-position Conventional hydrogen bond Halogen [Fluorine] Carbon hydrogen bond Pi-Sigma Alkyl, Pi-Alkyl
ZINC16319420	**-7.7**	ASP52 LYS27 LEU39 ILE60, ALA30	Conventional hydrogen bond Pi-Cation Pi-Sigma Pi-Alkyl
ZINC18196596	**-9.1**	LEU39 HIS40, ASP52 GLY51 LYS27 LEU42, VAL57	Amide Pi-Stacked Conventional hydrogen bond Carbon hydrogen bond Pi-Cation Pi- Alkyl
ZINC54201729	**-8.9**	HIS40, GLY43 THR53 LYS27, ARG36, ASP52 ILE46 LEU39, LEU42, ILE60, VAL57	Conventional hydrogen bond Carbon hydrogen bond Pi-Cation, Pi- Anion Pi-Sigma Alkyl, Pi-Alkyl

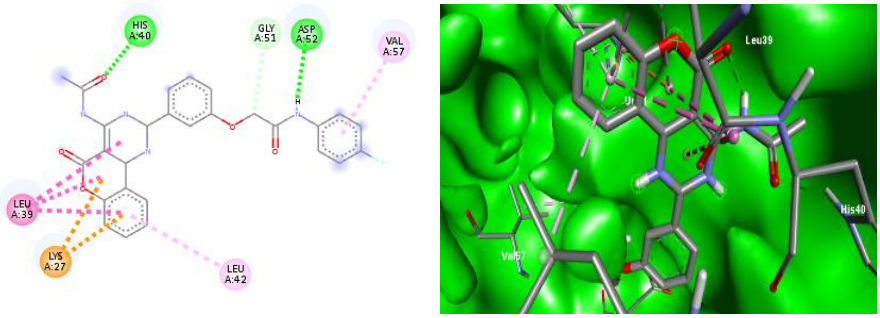

Fig1: 2D & 3D Interactions of ZINC18196596 with the protein 6xqi

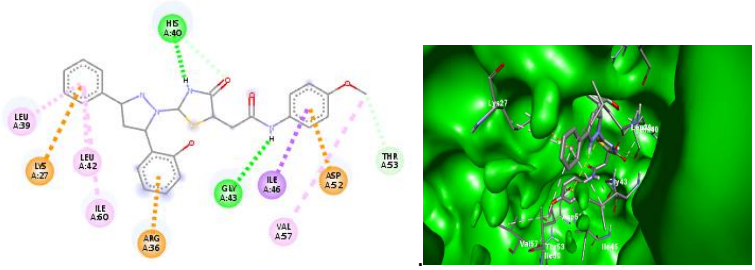

Fig 2: 2D & 3D Interactions of ZINC54201729 with the protein 6xqi

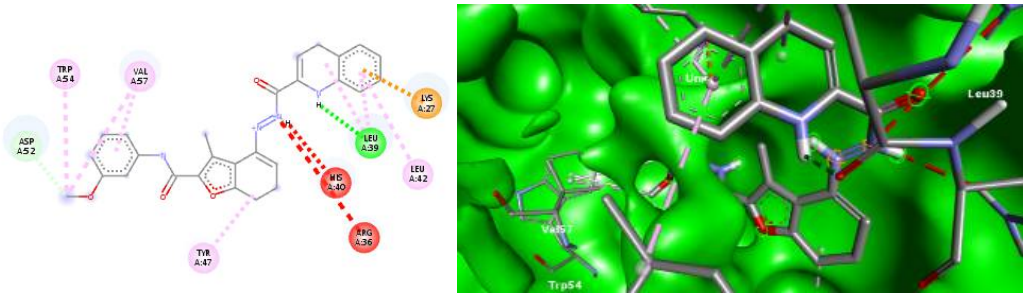

Fig 3: 2D&3D interactions of ZINC40825778 with the protein 6xqi

ADMET studies: A molecule's fate inside the body is largely determined by the ADMET characteristics. When a molecule is administered orally, a good absorption is sought. The distribution and absorption of a molecule throughout the system will be governed by the balance of lipophilic and hydrophilic groups in the structure. From a therapeutic standpoint, effectiveness and toxicity are important. The liver contains a variety of cytochrome enzymes that are responsible for the molecule's metabolism. As a result, after metabolization, the activity of the metabolite should be known and removed from the body when the intended therapeutic impact has been achieved using the PKCSM software to determine whether a molecule cluster has likeliness and to forecast the ADMET attribute. Lipinski rule of 5 for standard and ZINC compounds as shown in the table 3 &4

Table 3: Lipinski rule of 5 for standard compounds

Compound	MW	Rotatable bonds	H-bond acceptors	H-bond donors	XLOGP3
Tipranavir	613.803	11	7	4	2.8669
Amprenavir	720.962	17	9	4	5.9052
Darunavir	567.796	9	6	4	4.7476
Fosamprenavir	505.637	11	7	3	2.4028
Lopinavir	585.616	13	8	4	2.5198
Indinavir	628.814	15	5	4	4.3281
Ritonavir	704.869	14	9	5	4.2116
Nelfinavir	602.675	11	6	2	7.3255
Atazanavir	547.674	11	8	3	2.3753

Table 4: Lipinski rule of 5 for ZINC compounds

Compound	Molecular weight	Rotatable bonds	H-bond acceptors	H-bond donars	XLOGP3
ZINC40825778	468.513	5	6	2	4.8675
ZINC58881581	474.517	10	6	3	2.5217
ZINC2036593	476.242	5	6	3	3.4252
ZINC16319420	478.892	7	6	2	4.51702
ZINC18196596	498.47	6	7	2	4.5182
ZINC54201729	500.58	6	7	2	4.5787

CONCLUSION

The Idea of drug-likeliness serves as a helpful guide during the early stages of drug research.The number of hydrogen bond donors (HBDs) is five, the octanol/water partition coefficient (A log P) is five, and the number of hydrogen bond acceptors (HBAs) is five. 10 are Lipinski's first and best-known rule-based drug likelihood filters, which he introduced in 1997. The principle of 5 states that a compound could not be considered orally functional if it violated 2 or more of its four requirements. The "Rule of Five" and other drug-likeliness rules/filters were subsequently proposed. For instance, the above-mentioned study found that more than 90% of the compounds matched the following criteria: 2.5-4.5 [lop P], 450-500 [MW], hydrogen bond acceptor also got below 10 and hydrogen bond donor was below 5, based on the 7 molecules in the ZINC database from pharmacophore modelling. The drug-likeliness rules the process of developing drugs is improved by filtration based on physical and chemical characteristics, although there is research that demonstrates that these rules/ filters have their limitations. Based on the binding affinity and amino acid interaction eight ligands are subsequently evaluated for ADMET properties using PKCSM webserver. ZINC18196596 compound has good binding score and having good interaction with key amino acids of HIV has been identified for further development to treat HIV.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest.

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