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COMPUTATIONAL INSIGHTS ON ANTIVIRAL RESISTANCE MECHANISM OF HIV-1 PROTEASE WITH GS-8374

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ABSTRACT: Human immunodeficiency virus type 1 (HIV-1), is an etiologic agent of the most life-threatening disease AIDS. HIV-1 protease (HIVP) is a key enzyme that performs an essential step in the life cycle of the virus. HIV-1 protease assembled as a dimer in the functional form and involved in cutting "polyprotein" into the proper protein-sized pieces. The two chains assemble to form a long tunnel covered by two flexible protein forms a "flaps." The flaps open up, and the enzyme wraps around a protein chain, closing and holding it tightly in the tunnel. Highly active antiretroviral therapy (HAART) is the current successful treatment approach for AIDS and protease inhibitors plays a crucial role in HAART. The drugs that target against protease consider as one of the major approaches in modern medicine. Till date, 26 anti-HIV compounds have been approved by the Food and Drug Administration (FDA), and 10 are HIV protease inhibitors. The antiviral resistance occurs due to a point mutation in the viral protein which has been a big hurdle in the treatment of AIDS. To decipher the resistance mechanism of HIV-1 protease against current drug GS-8374, the computational studies have been carried out. The molecular docking analysis of protease mutants confirms the loss of crucial H-bonds with the drug that in-turn leads to antiviral resistance. In a nutshell, our studies can provide crucial structural insights on the resistance mechanism of HIV-1 protease against GS-8374.

INTRODUCTION: HIV-1 virus belongs to the family of retrovirus and one of the deadly etiologic agents of the human disease AIDS [1]. Till now, HIV infection is never cured and most challenging disease of a human. With the extensive scientific research carried out for the past two decades, 26 FDA approved antiviral drugs was reported and possess different mechanisms of drug action [2]. The current strategy of anti-HIV agents and treatment target suppression of viral load and patient is healthy. The development of HIV drug resistance is the major threat which reduces or even eliminates the efficacy of antiretroviral treatment [3].

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The key target HIV-1 protease is a viral aspartic protease which involved in cleavage of Gag and Gag-Pol polyproteins into individual functional proteins essential for viral maturation [4]. Drug discovery is majorly guided by the structure-based design based on a computational approach leads to the development of 10 FDA-approved protease inhibitors.

The successful inhibitors namely Amprenavir, Fosamprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir and Saquinavir against HIV-1 protease with active sites include residues Asp25 and Ile50 [5, 6]. Also, the inhibitors represent the potent anti-AIDS drugs reported till date and essential components of the therapy namely highly active antiretroviral therapy (HAART) [7]. Drug resistance to protease inhibitors is become a major issue and leads to HAART failure [8]. HIV-1 protease, asymmetric dimer, and both monomers contribute to substrate binding.

The critical active site region is primarily formed by residues 25-32, 47-53 and 80-84 [9] and solvent anchoring approach is used to develop protease inhibitors with improved resistance profile [10] and substitute a new lysine Sulfonamide-based molecular core [11]. The alternative strategy is mainly focussed on the substrate envelope constraints into the structure-based design and leads to novel potent protease inhibitors which are less susceptible to drug-resistance [12]. The major drug-resistant protease mutations are identified as conservative changes involving the gain or loss of a methylene group like I84V, V82I, V82A, I47V, and V32I mutations and also all possess significant impact in inhibitor binding [13]. The current clinical data and experimental studies been demonstrated with HIV-1 infection could be successfully treated with the minimized resistance mutations [14].

MATERIALS AND METHODS:

Dataset: The antiviral resistance mechanism against AIDS was studied by using the key drug target HIV-1 protease of HIV. The experimental 3D structure of wild HIV-1 protease with GS-8374 was download from PDB code 2I4W [15]. The 3D structure of 10 protease mutants was modeled using SPDBV [16] and energy minimization performed using Gromacs force field [17].

Molecular Docking: Molecular Docking is a computational method mainly used for identification of novel lead compounds and plays an integral part of drug discovery. AutoDock Vina[18] package available in PyRx software [19] was used for docking against HIV-1 protease. Both mutants and drug molecules were prepared for docking using AutoDockTools (ADT) in AutoDock. All the input files were saved in PDBQT format after minimization steps. The docking grid box was generated with the volume of 27000 Å was used for appropriate search space during the process. Blind docking was performed with box size 60 × 60 × 60 Å was used to target HIV-1 protease. The docking results were evaluated by least binding affinity in kcal/mol and number of hydrogen bond interactions with the drug. All visualization of docking results was analyzed using PyMOL [20].

RESULTS AND DISCUSSION: The experimental 3D structure of HIV-1 protease composed of dimer and consists of mostly Beta-strands and one alpha helix. The critical active sites involved in the substrate binding and function of protease. The drug target HIV-1 protease acts as one of the key targets for drug discovery and also a major role in HAART.

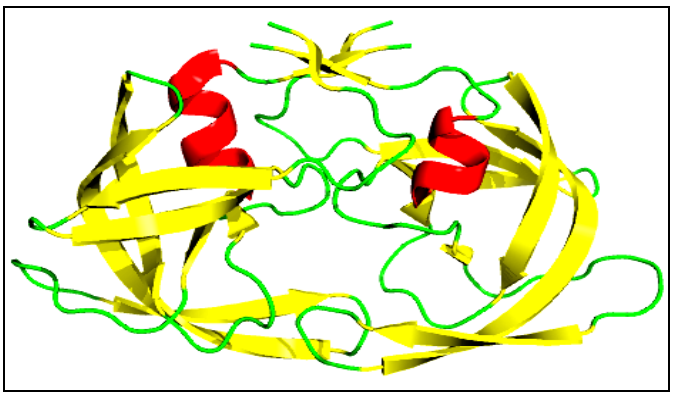

FIG. 1: EXPERIMENTAL 3D STRUCTURE OF WILD HIV-1 PROTEASE

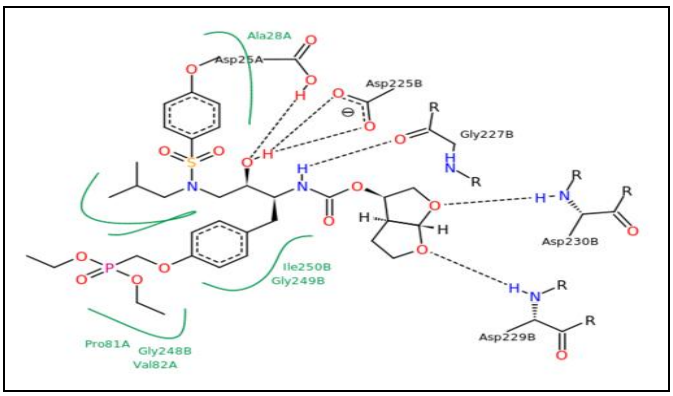

FIG. 2: HIV-1 PROTEASE-GS-8374 INTERACTION (PDB ID: 2I4W)

The drug GS-8374 is the recent one and identified with better inhibition against HIV-1 protease. The interaction confirmed the inhibition through hydrogen bonds involved by residues Asp25, Ala28, Asp225, Gly227, Asp308, and ASP298. Thus, the interaction with wild-type HIV-1 protease is important for the mechanism of inhibition and disruption in the key interaction leads to antiviral resistance.

Molecular Docking: Molecular docking was carried out for ten HIV-1 protease mutants against drug GS-8374 in AutoDock VINA to identify the binding conformation based on binding affinity. AutoDock results of hits showed ten conformations of docked complex and best pose was selected based on binding affinity. The top complexes were identified based on least binding affinity and number of hydrogen bonds.

The mutant I50L, I54L, V32I, and V82F showed less hydrogen bond interactions compared to wild-type protein composed of six hydrogen bonds and led to antiviral resistance. The other mutants are with unfavorable high binding affinity and hydrogen bonds with the critical residues shown in **Table 1**.

TABLE 1: DOCKING RESULTS FROM AUTODOCK VINA

S. no.	HIV-1 Protease Mutant	Binding Affinity (Kcal/mol)	Hydrogen Bonds
1	I50L	-8.4	1
2	I50V	-8.6	7
3	I54L	-8.6	3
4	I47V	-8.3	4
5	D30N	-8.9	4
6	L76V	-8.5	4
7	V32I	-9	3
8	V82F	-8.8	3
9	L33F	-8.8	4
10	G48M	-8.9	4

In the case of HIV-1 Protease mutant V32I with GS-8374 complex, the docking results showed three hydrogen bond interactions involved residues Arg8 and Ile50 of the active site. The atom pattern O2…CA of Ile50 with 4.06Å, O2…NH1 with 3.08Å and O2…NH2 with 3.12Å of Arg8 interacted.

In the case of HIV-1 Protease mutant V82F with GS-8374 complex, the docking results showed three hydrogen bond interactions involved residues Arg8, Ile50 and Asp229 of the active site. The atom pattern O2…CA of Ile50 with 4.12Å, O2…NH1 with 2.87Å OF Arg8 and O2…OD1 with 3.43Å of Asp229 interacted.

In the case of HIV-1 Protease mutant I54L with GS-8374 complex, the docking results showed three hydrogen bond interactions involved residues Arg8 and Ile50 of the active site. The atom pattern O2…CA of Ile50 with 4.07Å, O2…NH1 with 3.20Å and O2…NH2 with 3.22Å of Arg8 interacted.

In the case of HIV-1 Protease mutant I50L with GS-8374 complex, the docking results showed one hydrogen bond interaction involved residues Arg8 of the active site. The atom pattern O2…NH1 has interacted with hydrogen bond length 2.99Å.

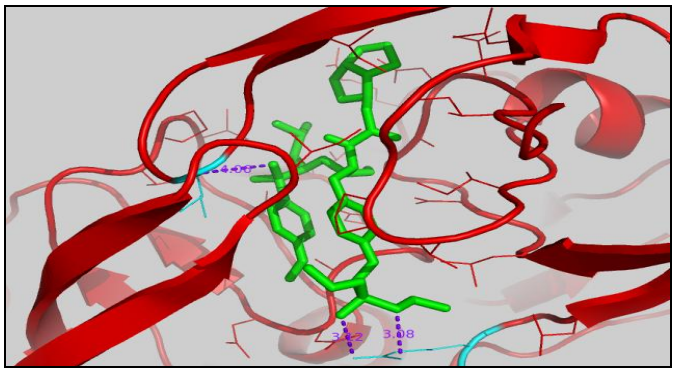

FIG. 3: HIV-1 PROTEASE MUTANT V32I WITH GS-8374

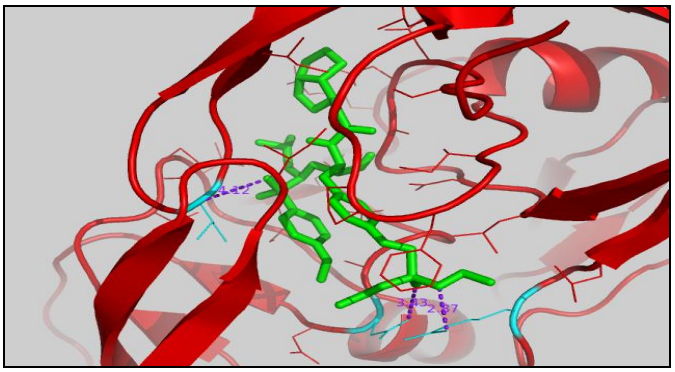

FIG. 4: HIV-1 PROTEASE MUTANT V82F WITH GS-8374

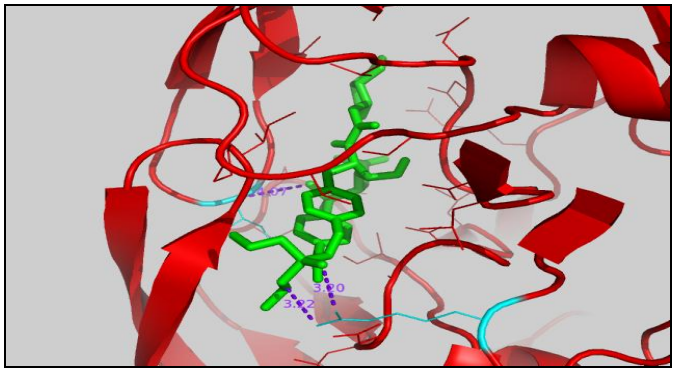

FIG. 5: HIV-1 PROTEASE MUTANT I54LWITH GS-8374

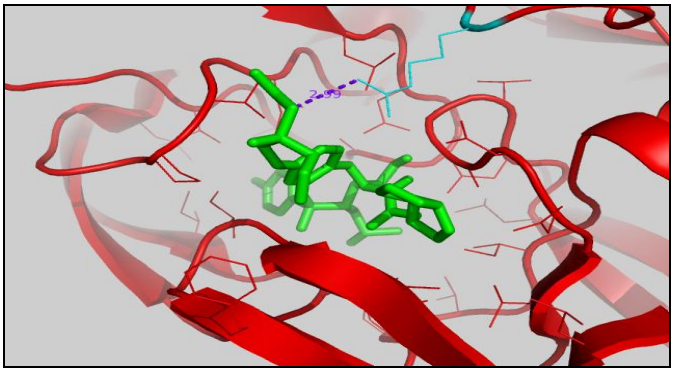

FIG. 6: HIV-1 PROTEASE MUTANT I50L WITH GS-8374

CONCLUSION: The computational approach was used to address the molecular mechanism of antiviral resistance of drug GS-8374 against HIV-1 protease mutants. The molecular docking study showed the hydrogen bond and hydrophobic interactions was missing in the mutant complexes compared to wild protein complex. The protease mutants I50V, I54L, V32I, and V82F formed fewer

hydrogen bonds and loss the critical interaction in favor of the inhibition. The mutant complexes loss the critical interaction pattern found in the wild protein complex. The major reason will be the conformation change in the HIV-1 protease due to a point mutation in the critical active sites. The mechanism of drug GS-8374 with mutants evaluated the antiviral resistance against AIDS. In conclusion, the computational study will be helpful to the biologist and clinicians to explore the specific mechanism of action. Further, molecular dynamics simulation and *in-vitro* experiments to analyze the resistance/susceptibility of drugs would be key aspects for future direction.

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CONFLICT OF INTEREST: The author declares there is no conflict of interest.

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