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Identification of Molecular Modelling and Structure Based Virtual Screening Approach

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ABSTRACT

The present workflow was designed to identify potential inhibitors for HIV-1 protease that is essential for the life-cycle of HIV. The in silico binding affinities of existing inhibitors namely Atazanavir and Ritonavir were compared using Glide module in Schrodinger suit 2013. Atazanavir was found to have the highest affinity towards HIV-1 protease. The structure based virtual screening on the basis of the binding modes of best inhibitor (Atazanavir) was performed and best scoring hits were identified.

Introduction

From an unprecedented wealth of information regarding the molecular biology and virology of HIV collected in recent years, it became possible to identify numerous intervention points in the viral life cycle that could be exploited in the development of drugs for AIDS therapy [1-3]. Among these, the virally-encoded enzymes, in particular protease and reverse transcriptase have emerged as the most popular targets [4]. HIV-1 protease is a retroviral aspartyl protease (retropepsin) that is essential for the life-cycle of HIV, the retrovirus that causes AIDS.

HIV protease cleaves newly synthesized polyproteins at the appropriate places to create the mature protein components of infectious HIV virions. Without effective HIV protease, HIV virions remain uninfectious. Thus, mutation of HIV protease's active site or inhibition of its activity disrupts HIV's ability to replicate and infect additional cells, making HIV-1 Protease inhibition the subject of considerable pharmaceutical research. HIV protease's protein structure has been investigated using X Ray Crystallography [5].

Materials and Methods

Selection of target and lead compound

Crystallographic structures of the target (HIV-1 Protease) was obtained from PDB (Protein Data bank) and saved in standard 3D coordinate format and was docked with inhibitors such as Ritonavir and Atazanavir, in order to get the most potential inhibitor based on their binding affinity. The best binding inhibitor was obtained and was searched for its 50% identical compounds. Small molecule libraries of 50 compounds, that are structurally similar to the drug Atazanavir were obtained from zinc database [17] and was docked with the enzyme, HIV-1 Protease. The potential hits were discovered and the lead compound was obtained for inhibition of the enzyme.

Graphical Visualization

The docked PDB structures of each inhibitor against the target were visualized and inspected for their goodness of fit and orientation inside the active site. This was done with Pymol (http://www.pymol.org/)andChimera (http://www.cgl.ucsf.edu/chimera/). Also the conformation and contacts with all amino acids were checked manually.

Result and discussion

For the docking study, protein (HIV-1 Protease) was prepared with potential energy of -821.977 and Root mean square deviation (RMSD) of 0.153511, which were obtained through the protein preparation wizard of Schrodinger Suit Version-9.7. Simultaneously, the zinc compounds taken from zinc database were prepared through LigPrep application. Table1 gives the information about the top 10. The table reveals that all the inhibitors satisfy the Lipinski's Rule.

The structure with least glide score was considered to be the best docked result.

The analysis of the docking results illustrates that Atazanavir had the lowest glide as well as docking score as compared to Ritonavir, and the other 50 compounds (similar to atazanavir) taken from zinc database.

The result analysis inferred that zinc compound ZINC03914596 had second highest binding affinity with a glide score = -11.8457. Theinhibitory activity of this compound can further beenhanced through mutations and modifications, which will make it stronger inhibitor against HIV- 1 Protease.

Docking was followed by molecular visualization of the docked complexes having best scores using the softwares like Pymol and Chimera.

Fig 1 (a & b) represents the docked structure of Atazanavir and ZINC03914596 with the protein HIV-1 Protease. It gives the pictorial representation of binding orientation of ligands with their receptor at the active site.

Fig 2 illustrates the interactions between the enzyme and best binding inhibitor (Atazanavir).

The interaction study illustrates that the binding site on the enzyme for the ligand is polar in nature because there are higher number of polar interactions between Atazanavir and the active site of the enzyme having residues like Asp, Arg and H2O molecules.

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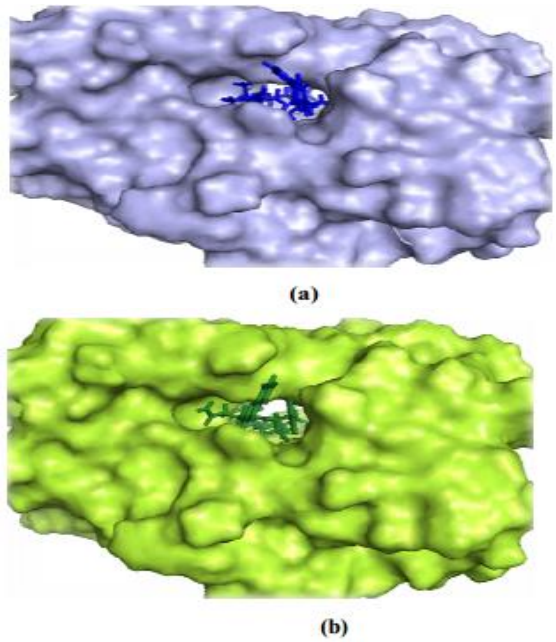

Fig 1. Docked structure of (a) Atazanavir and (b) ZINC03914596

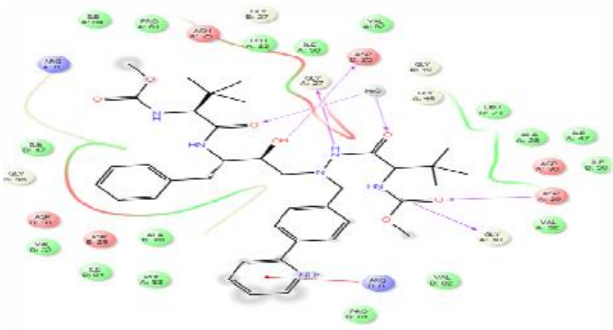

Fig 2. HIV1-Protease Interaction with Atazanavir

Conclusion

The present work emphasizes the study of protein inhibitor interactions which has a vital role in Computer Aided Drug Designing. Through virtual screening, hit compounds against HIV-1Protease were identified, which were used to obtain the lead compound via molecular docking. Simulation studies conclude that the observed conformational changes in the protease structure might have occurred due to the binding of the inhibitor molecule. This structure-based drug designing approach can be used to enhance more refined inhibitory property of novel lead molecules against HIV-1 protease that will aid knowledge in combating AIDS. This would hence be helpful to reduce the troubles of antibiotic resistance and also the drug's side effects as discussed earlier. In other words, through the above experimental study, we came to know that ZINC03914596 is a strong binding inhibitor of HIV-1 Protease enzyme.

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