ISSN (online): 2319-6599
ISSN (Print): 2319-6580

Comparing inhibiting activity of HIV-1 protease between Indinavir and its modifications using computational approaches

Ankur Saini[1], Ritika[2], Anita Grewal[3]*

[1,2,3]*Department of Biotechnology, University Institute of Engineering & Technology, Kurukshetra University, Kurukshetra, Haryana, India 136119*
sainiankur38@gmail.com[1], ritztiki@gmail.com[2], anitapunia_17@rediffmail.com[3]

Abstract

Objectives: To develop a potent anti-HIV agent
Methods: In the present study, two candidate ligand compounds-Pridyl methyl piperazine with acetamide and Urea derivative were designed using Chemsketch, by replacing –OH group based on indinavir as reference molecule. Designed ligands were tested *in silico* individually with HIV-1 protease enzymes. Rigid docking approach was applied to both the compounds by using Autodock, and qualitative inspection of the results was carried out.
Findings: Compound Modified 2 containing functional group pyridyl methyl piperazine with acetamide in place of hydroxyl group, and compound Modified 1 having urea derivative in place of hydroxyl group has shown potential bindings with HIV-1 protease enzyme. The Modified 2 showed better interactions in rigid docking method with an average lowest binding energy of -3.87 kcal/mol towards HIV-1 protease enzyme as compared to Indinavir which showed -3.52 kcal/mol lowest binding energy. However, the Modified 1' interactions were weak with an average lowest binding energy of +0.9 kcal/mol. In wake of the present work, it indicates that the compound Modified 2 which has been designed, has the tendency to interact with protease with efficient binding and emerges out as a potential candidate inhibitor of HIV-1 enzymes for further experimentation.
Application: Regardless of the drawbacks of chemical drugs such as its malignancy and lack of therapeutic effects, our study has shown that it is possible to produce more formidable potent anti-HIV agents.

Key words: Enzyme Docking, HIV-1, Protease, Chem-sketch, Indinavir, computational approaches, inhibiting activity

1. Introduction

Human Immunodeficiency Virus type-1 (HIV-1) belongs to the retrovirus family. It causes a life threatening disease for human immune system, known as the acquired immunodeficiency syndrome (AIDS)[1,2]. In order to complete its viral replication cycle, HIV-1 requires three different enzymes: (i) Protease (Figure 1) (ii) Integrase and (iii) Reverse Transcriptase [3], each having specific roles in the life cycle. HIV-1 reverse transcriptase enzyme acts by transcribing RNA of the HIV-1 virus into DNA. After the generation of viral DNA, it is integrated into the host genome by HIV-1 integrase enzyme[4]. After reverse transcriptase and integrase have carried out their respective tasks, HIV-1 protease enzyme will then follow[5]. Viral gene expression in host cell produces Env and Gag-Pol complex proteins. HIV-1 protease has a very important role as it helps in maturation by cleaving the viral polypeptides Gag-Pol into functioning structural and enzymatic proteins [6,7], which shows that polyprotein processing is not carried by host cell but by virus itself. Understanding working of HIV-1 enzymes, it explains that blocking activity of any one enzyme will hinder the life-cycle of HIV-1 virus. In the present study, we tried to inhibit the activity of protease enzyme which have been proved successful previously. But due to high-intrinsic toxicity of compounds and highly active resistant viral strains of HIV-1, it has been difficult to sustain their activeness towards HIV-1 [8,9,10].Structure of protease enzyme is dominated by *β*-strands and it has only one α-helix. In the present study, structural docking of HIV-1 protease enzymes was targeted for designing novel candidate molecules using Autodock. There are many available Inhibitors in market that have been approved by the Food and Drug Administration (FDA). These approved different antiviral agents can inhibit the HIV-1 enzymes. Some major antiviral agents includes indinavir, saquinavir, amprenavir, atazanavir, ritonavir and many more are under clinical trial[11]. Taking into consideration, the swift advancement of drug resistant variants culminates in transient drugs designed for clinical care, there is a dire need to evolve new antiretroviral drugs for wild-type and mutant strains of HIV-1 enzymes. The enzyme of HIV1, protease

ISSN (online): 2319-6599
ISSN (Print): 2319-6580

(PR) was investigated in this study. Based on the importance of functional groups from various studies previously done in this field, two new compounds were drafted by altering the already available commercial drug indinavir.

Figure 1. Monomer of HIV-1 protease (PDB ID: 4LL3)

Structure-Based Design Approach**:** Heterocyclic ring systems were used to impair pharmacokinetic properties, increase binding affinity, and provide innovative chemical scaffolds to oppose drug-resistant viral strains has proved to be an interesting approach. These scaffolds show many useful properties that make them important in designing a molecule. Heterocycles present in scaffold may directly bind to the enzyme, (by hydrogen bonds or hydrophobic interactions) which results in increased potential of drug[12]. It has been well known that the heterocyclic rings will play a major role in HIV-1 inhibitors due to their conformational restriction as well as their ability to acquire hydrophobic pockets and provide functionality for hydrogen bonding interactions. Already available inhibitor was taken and functional group was added to it to check its potency, scaffold of indinavir was taken and important functional groups were taken by analysing work conducted in this area of research and a new inhibitor was designed. Designed indinavir is modified by replacing one of the hydroxyl (-OH) group with potential side groups to improve its binding affinity towards selected key enzyme protease of HIV-1.

2. Methodology

2.1. Autodock

Through experimental methods, drug development is a rather expensive process and takes up a lot of time. In today's time, molecular docking using computational approaches has allowed one to reduce both the time and cost. In fact, this approach has been used to design and understand drugs at molecular level. In this study, rigid docking of enzymes with different ligands was performed by AutoDock software. The protein was kept as rigid. The ligands were kept flexible (different conformations). This software was used to calculate the binding free energy of enzyme-ligand interactions [13].

AutoDock's procedure to calculate the interaction between receptor and ligand is divided in steps: Formation of grid and Docking [14,15].

The first step is to retrieve required Ligand and Target.pdb files from major databases. The second step while using AutoDock 4.2 is preparing different file formats; (a) PDBQT format files for Target and Ligand (Target.pdbqt, Ligand.pdbqt), (b) Grid and (c) Docking Parameter file (a.gpf and a.dpf). The third step is to perform molecular docking using Cygwin and finally the results are analyzed. Autodock employs a stochastic Lamarckian genetic algorithm [16] for calculating ligand conformations and it also simultaneously minimizes its scoring function which indicates the thermodynamic stability of the ligand that is bound to the target protein [16, 17](Figure 2).

The use of experimental and bio-informatic techniques increases the success percentage in many stages of the discovery process. The application of AutoDock software in virtual screening is theoretically constrained by the features of chemical compounds that can be calculated. It is also constrained by relation between these features and the target [18].

In our study, we used autodock to carry out rigid docking between HIV protease 1 and indinavir, and also between the protease with the two modified compounds separately (Figure 3).

ISSN (online): 2319-6599
ISSN (Print): 2319-6580

Figure 2. Analysis results of interaction between protease and (A) Compound 1 (B) Compound 2 (C) Compound 3

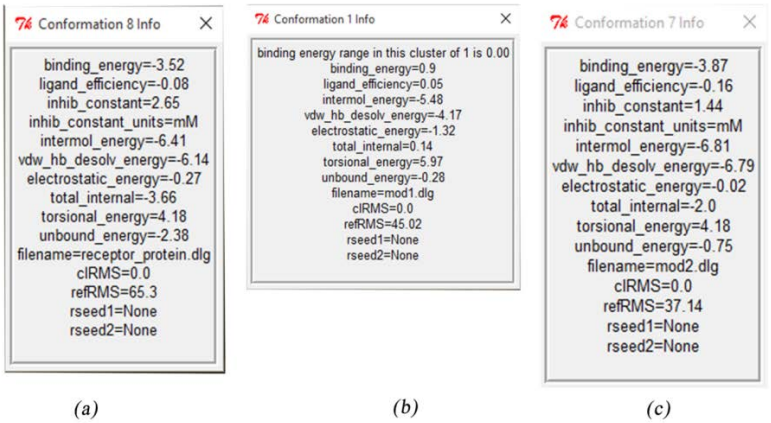
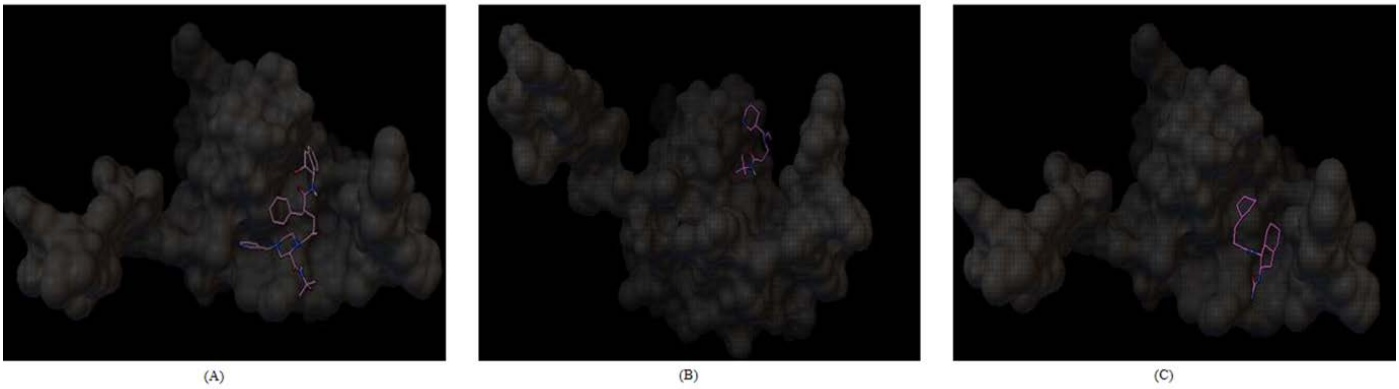


Figure 3. Interactions obtained of compounds with HIV-1 enzymes from AutoDock (rigid docking) approach. (A)Indinavir interactions with HIV-1 protease; (B) Modified 1 interactions with HIV-1 proteas; (C) Modified 2 interactions with HIV-1 protease.



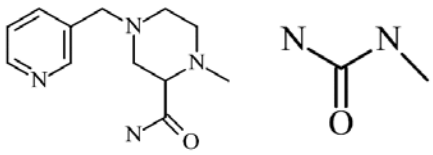
2.2. Chemsketch

Chemsketch program is used for molecular modelling to create images of chemical structures and modify them. Also, a software which displays two and three dimensions of molecules and molecular models, to perceive the structure of chemical bonds and the nature of the functional groups.

The program offers some advanced features that allow the molecules rotate and apply color to improve visualization. It has many other features like templates with functional groups and ions with the possibility to add text and use many other tools that can optimize structures created by the software.

In our study, we used chemsketch to make modifications in order to produce two distinct compounds. Compound Modified 1 having urea derivative in place of hydroxyl group, and compound Modified 2 containing functional group pyridyl methyl piperazine with acetamide in place of hydroxyl group has shown potential bindings with HIV-1 protease enzyme (Figure 4).

Figure 4. Pridyl methyl piperazine with acetamideUrea derivative



ISSN (online): 2319-6599
ISSN (Print): 2319-6580

3. Result and discussion

Indinavir and modified compounds were tested for rigid docking with HIV-1 protease enzyme. Upon observation, relevant and comparatively significant activity in docking with HIV-1 protease enzyme was seen. Replacing the hydroxyl (-OH) group in indinavir resulted in increased potency in compound (3) and decreased potency in compound (2) to interact with HIV-1 protease enzyme. Compounds were designed based on retrieving functional groups from research papers and adding those functional groups to indinavir. Mixed results in rigid docking were obtained and modified 2 could be considered as the best compound based on its binding energy towards HIV-1 protease enzyme (Table 1).

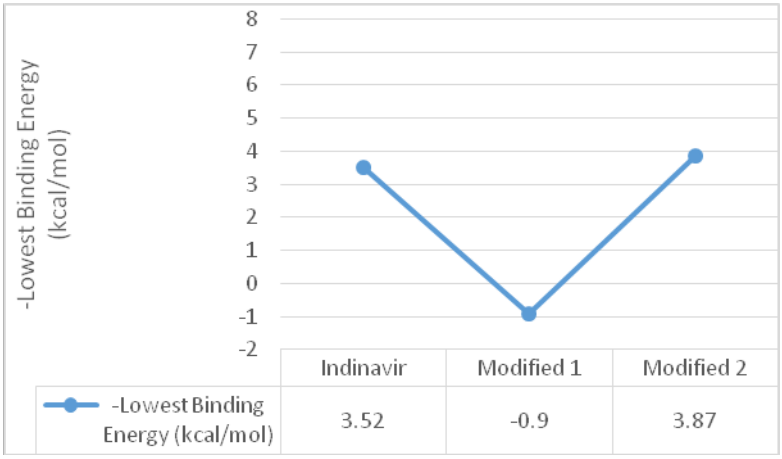
Table 1. Rigid docking results showing - lowest binding energy of all the compounds.

AUTODOCK RESULTS(Rigid Docking) Compound - Lowest Binding Energy (kcal/mol)	
(1) Indinavir	**3.52**
(2) Modified 1	**-0.9**
(3) Modified 2	**3.87**
*-Lowest Binding Energy = Negative Energy	

Rigid docking results state that (Table 1), Modified 2 could be considered as the best compound. Modified 2 were observed to be the most efficient towards HIV-1 protease enzyme in rigid docking as it showed the lowest binding energy. Modified 1 showed the highest binding energy from all the compounds compared in rigid docking approach towards protease. Indinavir showed significant interactions but was not as efficient as compared to Modified 2. Upon analyzation of the results obtained from rigid docking, it could be stated that compound (1) & (3) behaved positively towards protease but not compound (2).

Comparative study of results obtained from rigid docking shows that compound (3) has similar energy requirement as of indinavir towards protease but compound (2) shows a great amount of deviation (Figure 5).

Figure 5. Binding energies of compounds towards HIV-1 protease. Lowest binding energy obtained from rigid docking using AutoDock of each compounds with of HIV-1 protease enzyme (energy values in graph are negatively represented for Protease.)*



The best ranked compound (3) which has pyridyl methyl piperazine + acetamide in place of hydroxyl (-OH) group in indinavir, showed -3.87 kcal/mol lowest binding energy(AutoDock) towards HIV-1 protease enzyme. Compound that could be ranked after compound 3 is compound 1 which is indinavir that shows -3.52 kcal/mol lowest binding energy that is almost similar to our modified compound (3).

4. Conclusion

The approach which was followed to modify indinavir by adding functional groups, selected from different research studies and analysing its potency towards HIV-1 protease resulted in partial success. Modified 2 showed better interactions in rigid docking method than Indinavir but modified 1 interactions were weak.In rigid docking, Modified 2 which has pyridyl methyl piperazine with acetamide in indinavir in place of hydroxyl (-OH) group showed the average lowest binding energy -3.87 kcal/mol towards HIV-1 protease enzyme. Top ranked compound Modified 2 was modification of indinavir using functional groups from different studies, and this could be considered for further experimental studies to verify results obtained from this work.

5. References

1. M.Nielsen, S.Pedersen, J.Kjems. Molecular strategies to inhibit HIV-1 replication. *Retrovirology.* 2005; 2(10), 1-20.
2. E. Clercq. Toward improvement anti-HIV chemotherapy: therapeutic strategies for intervention with HIV-1 infections. *Journal of Medicinal Chemistry.*1998; 38, 2491-2517.
3. A. Pani, A. G. Loi, M. Mura, T. Marceddu, P. La Colla, M. E. Marongiu. Targeting HIV: old and new players. *Current Drug Targets-Infectious Disorders.*2002; 2(1), 17-32.
4. M. Coffin, H. Hughes, E. Varmus, P. Brown. Integration in retroviruses. ColdSpringHarbor Laboratory Press: New York, 1997.
5. H. Pearl, A. Taylor. A structural model for the retroviral proteases. *Nature.* 1997; 329, 351-354.
6. P. Darke, R. Nutt, S. Brady, V. Garsky, T. L. Ciccarone, P. Lumma, R. Freidinger, D. Veber, I. Sigal. HIV-1 protease specificity of peptide cleavage is sufficient for processing of gag and pol polyproteins. *Biochemical andBiophysical Research Communications.1988*; 156, 297-303.
7. S. Oroszlan, R. Luftig. Retroviral proteinases. *Currrent Topics in Microbiology Immunology.*1990; 157, 153-185.
8. F. Schinazi, I. Hernandez-Santiago, J. Hurwitz. Pharmacology of current and promising nucleosides for the treatment of human immunodeficiency viruses. *Erratum Antiviral Res.*2006; 71, 322-334.
9. B. Young, D. Kuritzkes. Resistance to HIV-1 protease inhibitors. *Infectious Disease andTherapy.*2002; 25, 257-282.
10. L. Bacheler. Resistance to non-nucleoside inhibitors of HIV-I reverse transcriptase. *Drug Resistance Updates.*1999; 2(1), 56-67.
11. G. Barbaro, A. Scozzafava, A. Mastrolorenzo, C. Supuran. Highly active antiretroviral therapy: current state of the art, new agents and their pharmacological interactions useful for improving therapeutic outcome. *Current Pharmaceutical Design.*2005; 11, 1805-1843.
12. K. Ghosh, D. Anderson. Tetrahydrofuran, tetrahydropyran, triazoles and related heterocyclic derivatives as HIV protease inhibitors. *Future Medicinal Chemistry.*2011;3(9), 1181-1197.
13. D. Goodsell, J. Olson. Automated docking of substrates to proteins by simulated annealing. *Proteins: Structure, Function, and Bioinformatics.*1990; 8, 195-202.
14. D. Goodsell, G. Morris, A. Olson. Automated docking of flexible ligands: Applications of AutoDock. *Journal of Molecular Recognition.*1996; 9, 831-835.
15. Using AutoDock 4 and AutoDockVina with AutoDockTools: A Tutorial. http://autodock.scripps.edu/. Date accessed: 10/10/2015.
16. G. Morris, S. Goodsell, S. Halliday, R. Huey, E. Hart, K. Belew, J. Olson. Automated docking using a Lamarckian genetic algorithm and empirical binding free energy function.*Journal of Computational Chemistry.*1998; 19, 1639-1662.
17. G. Morris, R. Huey, W. Lindstrom, F. Sanner, K. Belew, S. Goodsell, J. Olson. AutoDock4and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of Computational Chemistry*.2009; 30, 2785-2791.
18. M. Lazarova. Virtual screening-models, methods and software systems. *International Scientific Conference Computer Science*. 2008; 55-60.

The Publication fee is defrayed by Indian Society for Education and Environment (iSee). www.iseeadyar.org
Cite this article as:

Ankur Saini, Ritika, Anita Grewal. Comparing inhibiting activity of HIV-1 protease between Indinavir and its modifications using computational approaches*. Indian Journal of Bioinformatics and Biotechnology.* Vol 4 (3), August, 2016.