Journal of Computational Methods in Molecular Design, 2012, 2 (1):39-43

Scholars Research Library
(http://scholarsresearchlibrary.com/archive.html)

ISSN : 2231- 3176
CODEN (USA): JCMMDA

Docking Analysis of Darunavir as HIV Protease Inhibitors

Manikrao A. M., Mahajan N. S., Jawarkar R. D., Khatale P. N., Kedar C. K.* and Thombare S. K.*

Department of Pharmaceutical Chemistry, Sahyadri College of Pharmacy, Methwade, Sangola, Solapur.Maharashtra, India

---

ABSTRACT

Acquired immune deficiency syndrome (AIDS), caused by HIV virus, is one of the world's deadly disease with significant impact on the modern world. The present investigation aims to assess the binding mode of Darunavir with HIV protease inhibitor and role of water in drug receptor interaction by using docking analysis. Docking analysis revealed that, carbonyl oxygen, sulfonyl oxygen, amino nitrogen and furan oxygen are actively involved in electrostatic interaction with HIV protease. Carbonyl oxygen elicit hydrogen bonding with AspB25 (% of H- bonding is 65% and interatomic distance 2.8 A^0), AspA25 (% H-bonding 42% and interatomic distance 2.59A^0) whereas furan ring oxygen form H-bond with AspB30 (% H-bonding 11% and interatomic distance 3.42 A^0). To analyse the close contact of Darunavir and HIV protease, we have recorded the drug receptor interaction within four A^0. Noticeably, both oxygen of sulfone elicit hydrogen bonding with IleA50 and IleB50 through water. Subsequently, amino nitrogen form H-bond with AspA30 through the involvement of water. The present docking analysis concluded that Darunavir interact with HIV protease through hydrogen bonding where involvement of water in drug receptor interaction serves as evidence for the future development of new protease inhibitor.

INTRODUCTION

HIV-1 protease has been an important drug target for the antiretroviral treatment of HIV infection. Human immunodeficiency virus type 1 (HIV-1) protease is essential for cleavage of the viral gag and pol polyproteins, releasing both structural and enzymatic proteins necessary for viral maturation.[1,2] Since inhibition of the HIV protease function will prevent the maturation of these viral proteins and thus the replication of the virus,HIV-1 protease has been an important target of AIDS therapy. Currently, there are nine Food and Drug Administration(FDA)-approved

protease drugs: saquinavir (SQV), ritonavir (RTV),indinavir (IDV), nelfinavir (NFV), amprenavir (APV), lopinavir (LPV),atazanavir (AZV), tipranavir (TPV), and darunavir (TMC114).In present investigation ,we are reporting binding mode of darunavir with HIV-1 Protease.(figure 1)

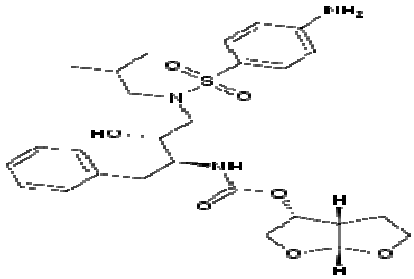
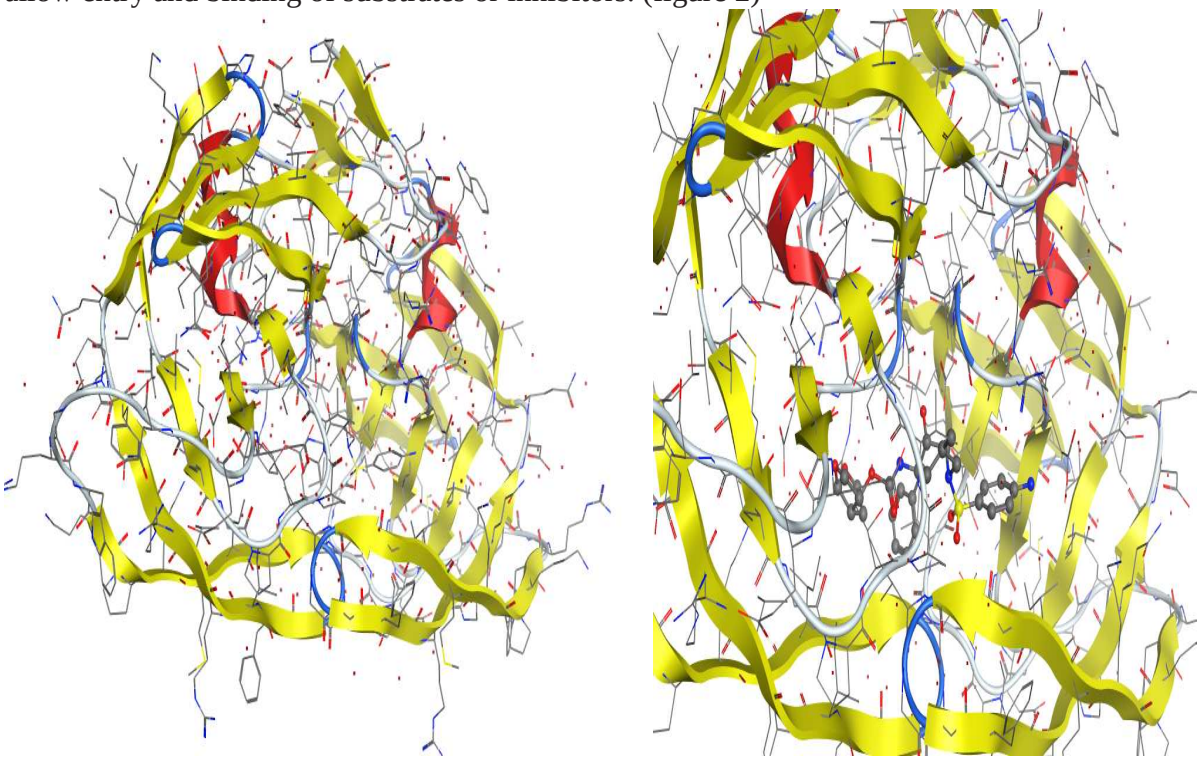


Figure 1 showing structure of darunavir.

Structure of HIV-1Protease

Protease is a homodimeric aspartic protease and its substrate binding pocket includes the Asp25 (25')-Thr26(26')-Gly27(27) catalytic triad and flap regions, which presumably open and close to allow entry and binding of substrates or inhibitors. (figure 2)



Structure of HIV-1 Protease **Structure of HIV-1 Protease with darunavir**

Figure 2 showing structure of HIV-1 protease virus.

Molecular modelling

Docking analysis was performed by molecular operating environment. Three dimensional structure of darunavir was prepared by Chemdraw 3D ultra software.3D structure of HIV-1 Protease was obtained from protein data bank. Conformational analysis was performed by Hyperchem 9.0.Lowest energy conformation was selected for docking

RESULTS AND DISCUSSION

Hydrogen bonding Interaction

Darunavir interact with HIV-1 protease through hydrogen bonding, hydrophobic and Vander Waals interactions. Docking analysis revealed that, carbonyl oxygen, sulfonyl oxygen, amino nitrogen and furan oxygen are actively involved in electrostatic interaction with HIV protease. Furan oxygen act as hydrogen bond donor, carbonyl oxygen act as hydrogen bond acceptor in drug receptor interaction. Carbonyl oxygen elicit hydrogen bonding with AspB25 (% of H-bonding is 65% and interatomic distance 2.8 A^0), AspA25 (% H-bonding 42% and interatomic distance 2.59A^0).

Furan ring oxygen form H-bond with AspB30 (% H-bonding 11% and interatomic distance 3.42 A^0).Amino nitrogen form H- bond with AspA30 through the involvement of water. Hydrogen bonding interactions are shown in figure 3.Role of water is crucial in deciding drug receptor interactions.

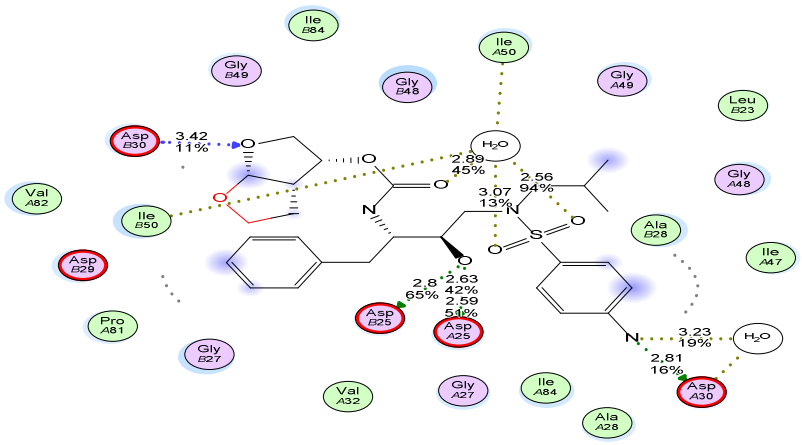


Figure 3 showing Hydrogen bonding interaction Darunavir and HIV-1 protease virus.

Vanderwaals Interactions

Elements of the surface are drawn if they are within a certain distance of a ligand atom; by default, the distance is 8 Å. The interactions which occurs at a distance of 8 Å are referred as Vanderwaals Interactions. The Interaction Surface identifies steric hindrance in the active site. It is a 0-potential energy contour of the van der Waals potential of a probe atom with the receptor. The interior of the 0-potential energy surface contains those locations at which the probe van der Waals energy is positive; the exterior has negative interaction energy. Thus, if a non-hydrogen atom nucleus crosses the surface near the receptor Vander Waals repulsion will occur. Vander Waal interactions are shown in figure 4.

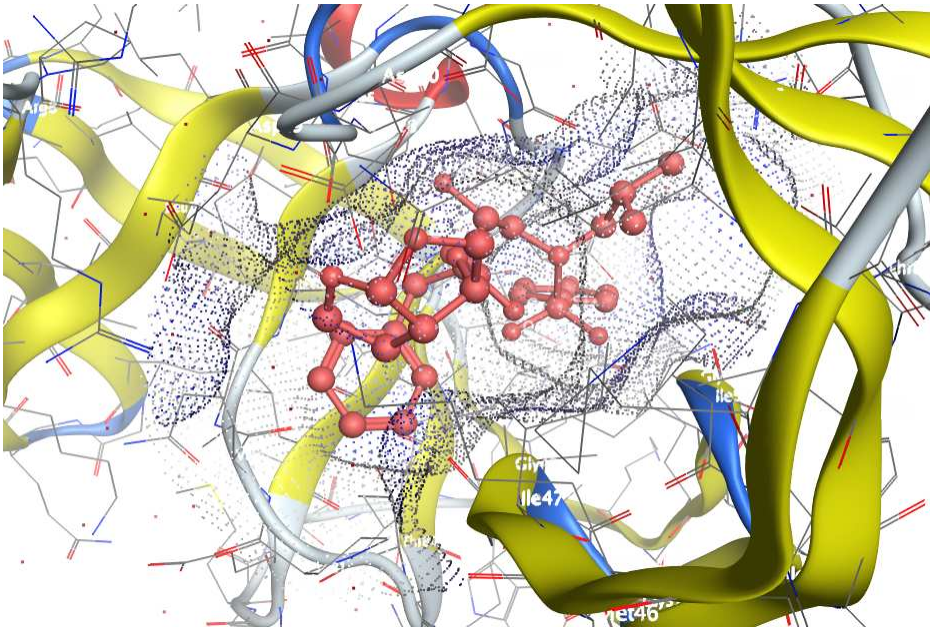


Figure 4 showing Vanderwaal surface around Darunavir

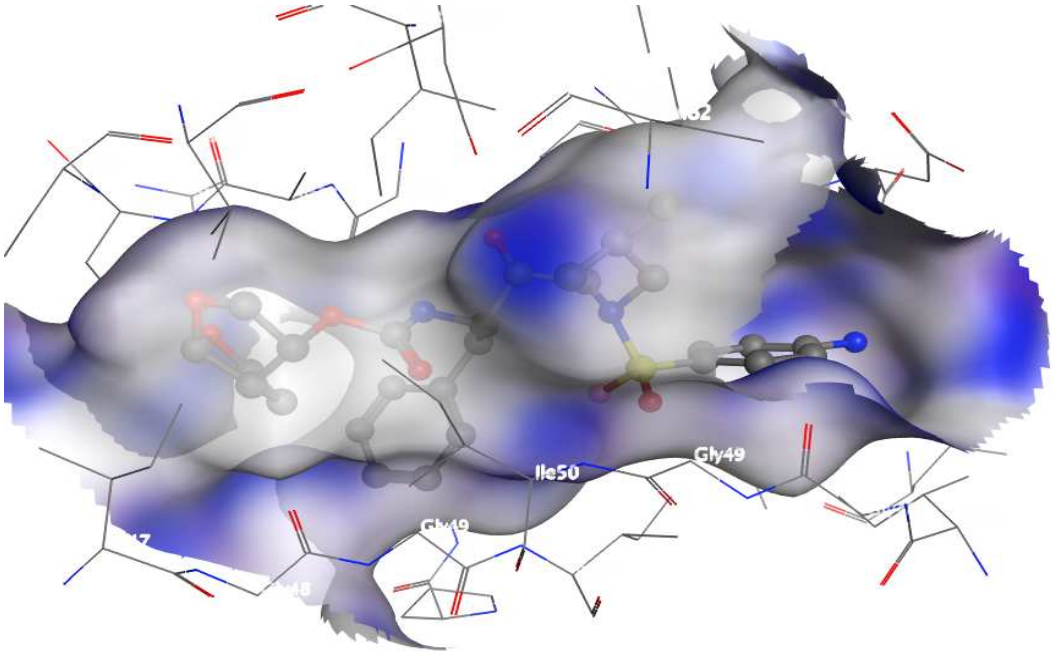


Figure 5 showing Surface interactions of Darunavir and HIV-1 protease virus.

Surface interaction of Darunavir and HIV-1 Protease

Surface interactions are shown in figure 5.Darunavir fitted well into the binding of HIV-1 protease virus. It acquire extended conformation within the receptor pocket. Terminal benzene ring is in close proximity with the hydrophobic surface of receptor. Second benzene ring near

amide linkage align on the flat hydrophobic surface of receptor which intend that benzene ring may be involved in Vander Waal interactions. Further furan ring is in close contact with the hydrophobic region of receptor.

REFERENCES

[1] Darke PL, Nutt RF, Brady SF, Garsky VM, Ciccarone TM, Leu CT, Lumma PK, Freidinger RM, Veber DF, Sigal IS. *Biochem Bioph Res Co* **1988**;156:297–303.
[2] Kohl NE, Emini EA, Schleif WA, Davis LJ, Heimbach JC, Dixon RAF, Scolnick EM, Sigal IS. *Proc Natl Acad Sci USA* **1988**;85:4686–4690.