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Case Report
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The Extension of the Binding Pocket in HTLV-1 Protease

Masoud Keikha[1,2]*

[1]Department of Antimicrobial Resistance Research, Mashhad University of Medical Sciences, Iran

[2]Department of Microbiology and Virology, Mashhad University of Medical Sciences, Iran

Editorial

HTLV-1 virus is a member of the retroviruses containing positive polarized, single-stranded RNA that is classified as delta-viruses. HTLV-1 is a causative agent of lethal infections such as Adult T-cell Leukemia/Lymphoma (ATLL) and HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) [1]. Like other retroviruses, HTLV-1 virus also contains the gag, pol and env genomes. Proteases, reverse-transcriptase and integrase enzymes are encoded by the pol gene, which also play a very important role in the pathogenesis of HTLV-1 [2]. HTLV-1 protease (HTLV-1 PR) enzyme is one of the most important enzymes involved in the process of replication and maturation of HTLV-1 virus, classified at its active site in the aspartic proteases group due to the presence of two residues of aspartic acid (Aspartic acid 32/36) [2,3]. HTLV-1 PR is a homodimer, each sub-unit of which contains 125 residues. The enzyme is r-responsible for the cutting and processing of gag-pro-pol and gag polyprotein, which contains multiple cutting sites in the matrix/capsid, capsid/nucleocapsid, gag/protease and p3/protease [3,4].

HTLV-1 PR enzyme is one of the most important molecular targets for the treatment of HTLV-1 [2]. Due to the similarity of 45% of the active amino acid sites of HTLV-1 and HIV-1 proteases, it is believed that HIV-1 protease inhibitors may also inhibit HTLV-1 PR activity. Based on the in vitro studies and crystallographic structure investigations, it has also been shown that HIV-1 protease inhibitors can attach to the active sites of HTV-1 PR and inhibit the enzyme activity. In addition, researchers have developed peptidomimetic compounds for inhibiting HTLV-1 PR, and some of these structures have yielded satisfactory results [2,4,5].

However, specific and effective drug combinations for HTLV-1 have not been introduced yet and HTLV-1 infection cases are treated with Zidovudine plus IFN-α [2]. Considering the necessity of developing studies on the introduction of effective treatment options against HTLV-1, this study aimed to introduce a new approach regarding the design of HTLV-1 PR specific inhibitors by analyzing the joint ligands connected to HTLV-1 PR.

In this study, all of the crystallographic structures of HTLV-1 PR were obtained from the Protein Data Bank database (PDB), which included 2B7F, 3LIN, 3LIQ, 3LIT, 3LIV, 3LIX, 3LY, 3WSJ, 4YDF and 4YDG. Then, attempts were made to locate the ligand binding site to the HTLV-1 PR enzyme through superimposition of the ligands (Figure 1). Studies have shown that most of the common areas in the central area are active site of enzymes and are very close to aspartic acid 32 and 36 residues; however, some ligands, especially peptidomimetic, were outside the active site of the HTLV-1 PR enzyme.

The proposed binding site coordinates were as X=88.99, Y=55.11 and Z=54.27, and Radius=10,000,000 (based on the 2B7F structure). Considering that this place is located in the center of the active site and is very close to the aspartic acid residue, it seems that compounds designed according to the physicochemical properties of this area are likely to not lose efficacy in mutant strains.

In the next step, the molecular docking was done for all the extracted ligands from the HTLV-1 PR crystallography structures in the designed binding site and, through the molecular docking assessments, it was determined that all of the ligands have the ability to bind to the HTLV-1 PR enzyme via the designed binding site, such that the binding energy levels for some of the compounds, especially "Indinavir", became better than their primary binding pocket. Modeling studies also indicated that the "Indinavir" spatial arrangement in the new binding pocket displaced about 3.5Å, so that the orientation of the "Indinavir" catalytic groups was also found in the new binding pocket, which provided the binding capacity of this drug to more numerous residues as compared to the primary state (Figures 2 and 3).

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***Correspondence:**
Masoud Keikha, Department of Microbiology and Virology, Mashhad University of Medical Sciences, Mashhad, Iran, Tel: 09386836425; E-mail: masoud.keykha90@gmail.com

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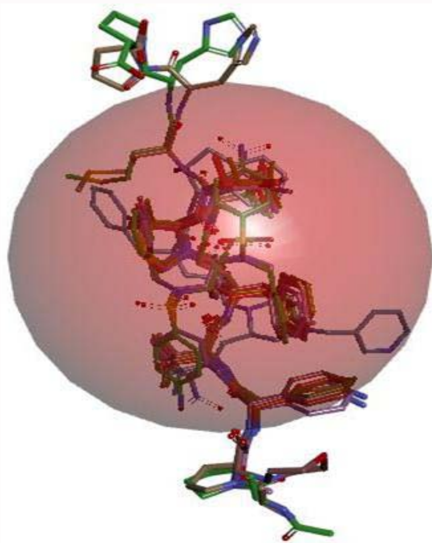

Figure 1: The spatial range of common ligands region.

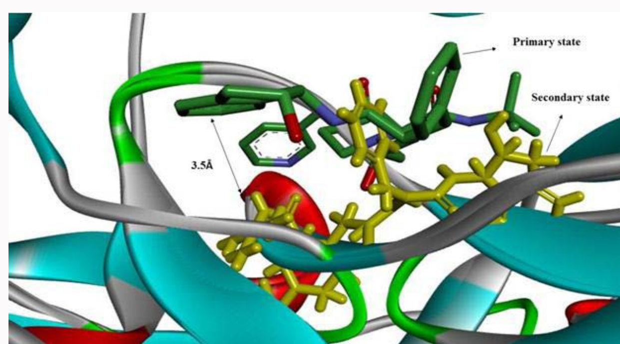

Figure 2: The 3D orientation changes of Indinavir in novel binding pocket.

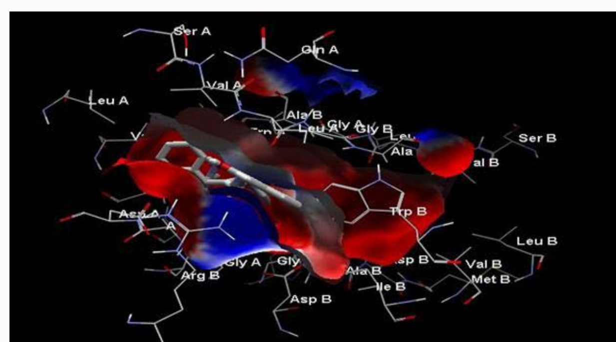

Figure 3: The Indinavir and surrounded residues in novel binding pocket.

There is currently limited information available on the HTLV-1 PR enzyme. As our wider knowledge of this enzyme and its second catalyst, we can design more specific and effective therapeutic options. It was tried in this study to provide a new area for designing the new compounds with greater binding power to the HTLV-1 PR enzyme by considering the HTLV-1 PR inhibitor joint interfaces. This area is in the center of the active region and close to catalytic residues, especially aspartic acids 32 and 36, and therefore the drugs that are designed according to our proposed area are more resistant to point mutations.

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References

1. Iqbal M, Reljic T, Sher T, Ayala E, Murthy H, Bazarbachi A, et al. Assessing the Efficacy of Allogeneic Hematopoietic Cell Transplantation in HTLV-1-Associated Adult T-Cell Leukemia/Lymphoma: Results of a Systematic Review/Meta-Analysis. Biol Blood Marrow Transplant. 2019;25(3):S388.
2. Soltani A, Hashemy SI, Avval FZ, Soleimani A, Rafatpanah H, Rezaee SA, et al. Molecular targeting for treatment of human T-lymphotropic virus type 1 infection. Biomed Pharmacother. 2019;109:770-8.
3. Kádas J, Weber IT, Bagossi P, Miklóssy G, Boross P, Oroszlan S, et al. Narrow substrate specificity and sensitivity toward ligand-binding site mutations of human T-cell Leukemia virus type 1 protease. J Biol Chem. 2004;279(26):27148-57.
4. Naka H, Teruya K, Bang JK, Aimoto S, Tatsumi T, Konno H, et al. Evaluations of substrate specificity and inhibition at PR/p3 cleavage site of HTLV-1 protease. Bioorg Med Chem Lett. 2006;16(14):3761-4.
5. Zhang J, Balestrieri E, Grelli S, Matteucci C, Pagnini V, D'Agostini C, et al. Efficacy of 3′-azido 3′ deoxythymidine (AZT) in preventing HTLV-1 transmission to human cord blood mononuclear cells. Virus Res. 2001;78(1-2):67-78.