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Original Article

The Indinavir Derivate as a Novel Pharmacophore for Treatment of HTLV-1 Viral Infections

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Abstract

Background and Aims: Human T-lymphotropic virus type 1 (HTLV-1), is as a type C retrovirus, which was first isolated from a patient with Adult T-cell leukemia/lymphoma (ATLL). Approximately 10-20 million people are infected by HTLV-1 virus worldwide, but only 5-10% of them develop clinical manifestations such as Acute-T lymphoma (ATL), HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), uveitis, and infective dermatitis. Indinavir was the first protease inhibitor used for treating HIV-1. It has some activity on HTLV-1, but it is not fully able to inhibit the HTLV-1 protease. Nowadays, design and construction of novel pharmacophore compounds can serve as an appropriate replacement for Indinavir.

Materials and Methods: In the present research, we used bioinformatics studies, to evaluate the potential role of four novel pharmacophres with inhibitory function on HTLV-1 protease, so called KMI pharmacophores (Keikha Modified Indinavir).

Results: After a detailed structural analysis of each of them, it seems all four designed phamacophores, (especially KMI-3) could be more effective on HTLV-1 protease than Indinavir.

Conclusions: According to exact in silico evaluations of each four pharmacophores, KMI-3 demonstrated a potential for its use on treatment of HTLV-1 infections.

Keywords: HTLV-1; Protease; Indinavir; Molecular docking.

Introduction

The Human T-lymphotropic virus type 1 (HTLV-1) was first isolated by Poiesz et al. from an American young black with cutaneous T cell-lymphoma [1]. HTLV-1, is a human deltaretrovirus type C, and belong to Orthoretrovirinae subfamily [1-2]. So far, four different types of HTLV virus have been identified, and HTLV-1 is the most prevalent type [3]. HTLV-1 infects approximately 10-20 million people worldwide, 90% of them are asymptomatic HTLV-1 carriers. Nonetheless, only 5-10% of them will develop HTLV-1 associated disorders such as Acute-T leukemia/lymphoma (ATLL), HTLV-1 associated myelopathy/tropical spastic para-paresis (HAM/TSP), HTLV-1 associated dermatitis, and HTLV-1 uveitis [3].

The most HTLV-1 endemic areas are South of Japan, Caribbean basin, central Africa, South America, Melanesian islands, and Iran (especially Mashhad) [2-3]. HTLV-1 infection

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is transmitted by breastfeeding, sexual contact, and receiving blood or blood products [4-5]. Despite the long time since HTLV-1 discovery, and the large number of HTLV-1infected individuals there is no effective drug against the virus, so far.

In contrast, there are many active drugs against HIV and HCV, capable of controlling HIV viremia, or providing cure, in the case of HCV [6]. Drugs like Zidovudine (ZDV), and interferon-α (IFN-α) are recommended to treat patients with ATLL [6-7]. However, some available studies show a limited activity of AZT on HTLV1-1 infection [8].

The structural differences between HIV and HTLV-1 enzymes are known as the main cause of the lack of efficacy of anti-HIV-1 drugs on HTLV-1. In addition, HTLV-1 able to integrate its genome into the host genome, and usually proliferates by clonally, via duplication of infected cellules. So, targeting effective signaling routes in HTLV-1 pathogenesis, based on the structure of viral enzymes seems to be the best strategy for designing anti-HTLV-1 drugs [6,9].

The HTLV-1 protease (PR) has a pivotal role in propagation and maturation of virus. This enzyme is a homodimer aspartic protease (presence of two Aspartic amino acids in the positions 32 and 36 of active site), and each chain is formed of 125 amino acid residues. The enzyme is responsible for processing of Gag-pro-pol, and Gag polyproteins, which in turn have key role in virus maturation [10].

Like HTLV-1, other viruses such and HIV viruses have specific proteases each. Many protease-inhibitors have been used to treat HIV and HCV, like. Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, and Ritonavir, (for HIV)or Asunaprevir, Boceprevir, Grazoprevir, Paritaprevir, Simeprevir, Telaprevir (for treatment of HCV) [6,11]. Considering similarity of spatial shape of HTLV-1 and HIV proteases, is valid to hypothesise that anti-HIV protease inhibitors are also effective for HTLV-1 infection.

Indinavir was approved by FDA in March 1996, but is no longer in use for treating HIV infections. However, it's in vitro activity against HTLV-1 was [12]. Based on Selvaraj et al. studies, the main reason for the absence of anti-HTLV-1 activity of HIV-1 protease inhibitors is the presence of a Methionine 37 at active site of HTLV-1 protease [13].

Currently, development in pharmacophore field, is considered as the most important approaches in design and synthesis of drugs. In pharmaceutical studies, such approach allows professional designing at lower costs, by using specific softwares and existing patterns, making easy and by initial screening by docking's software analysis and further synthesis of the best compound for testing [14]. The main goal of this study was designing and evaluation of molecular docking of Indinavir-derived pharmacophores against HTLV-1 PR.

Methods

The low efficacy of Indinavir against HTLV-1 PR, is expected due to the differences in aminoacids sequences in active sites of HTLV-1 and HIV-1 proteases. We retrieved crystallography structure of HIV-1 PR (2UXZ) and HTLV-1 PR (3WSJ) from PDB database (www.rcsb.org). Superimposition was done to investigate structural differences of enzymes, and aminoacids sequence of enzymes was aligned by Geneious software to determine their differences and active sitesThe interaction ratio between Indinavir and HTLV-1 PR was then evaluated by LIGPLOT software. In the next stage, Indinavir structure was taken from Pubchem (https://pubchem.ncbi.nlm.nih.gov/) web site, and optimized in terms of energy via Hyperchem software and MM3+ algorithm. The docking process was performed using Molegro virtual docker software, and evolutionary algorithms method [15]. Orientations of docked ligand (Indinavir) was compared to crystallography of HTLV-1 PR in complex with Indinavir (3WSJ). The root-mean-square deviation (RMSD) of closest orientation of docking results with crystallo-graphy structure was evaluated 157 Å (angstrom). Finally, using hydrophobic properties, H-bond, and Electric charge of residues in the binding packet of drug, four pharmacophores were suggested. The pharmacologic, toxic, and carcinogenic

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properties of designed pharmacophores were assessed by online websites such Molinspiration (www.molinspiration.com), Lazar (https://lazar.in-silico.de/predict), and Swiss ADME. Each of pharmacophores were separately optimized, and docking analysis in protease active site was done with coordinates X=39.31, Y=0.60, and Z=24.83 in radius=10.

Results

To review and compare the three dimensional structure, and enzyme active sites in HIV-1 and HTLV-1, crystallography construction of both proteins was superimposed, and their amino acid sequences was aligned (Figures 1a, and 1b). According to alignment results, the rate of sequence similarity was estimated as 38% (Figure 1b). Contrary to differences found in the three-dimensional structure and amino acids position in HTLV-1 and HIV-1 proteases, the active site is preserved in both viruses, and 95% similarity was seen (Figure 1b). Notwithstanding, there is a fundamental difference between two viral proteases; HIV-1 protease has 99 amino acids, while HTLV-1 protease 116 amino acids. This difference is as the main factor for failure in treatment, and lack of effective act of anti-HIV proteases against HTLV-1 PR. Studies have shown, there are two main differences between HTLV-1 and HIV-1 proteases: first, presence of some unique amino acids, in the functional domains of HTLV-1 PR, such as Met37, Ser55, Val56, Leu57, and Ala59; second, some amino acids in functional domains of HTLV-1 PR, such Arg10, Leu23, Asp25, Gly27, Asp29, Asp125, Ala128 and Thr131, which are also in HIV-1 PR sequence, but in different positions than their positions in HTLV-1 PR.

These differences lead to the ineffectiveness of Indinavir against HTLV-1 PR. As a general conclusion, in order to more efficacy of this drug on HTLV-1 PR, structural changes must be done on it.

A detailed review shows that there is a relatively weak bond between Indinavir and HTLV-1 protease enzyme (Figure 2).

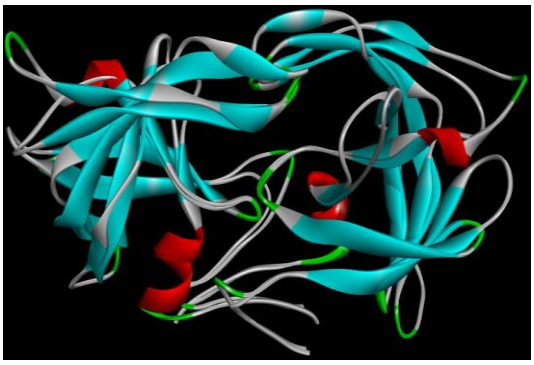


Fig. 1a. Superimposition of HTLV-1 PR vs HIV-1 PR.

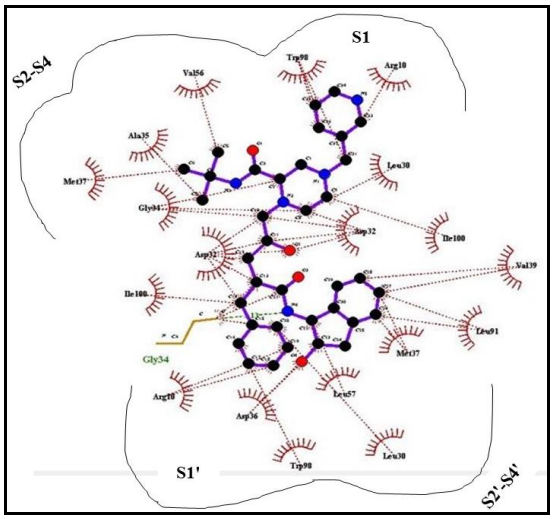


Fig. 2. Indinavir interaction with S1, S2-S4, S1' and S2'-S4' pockets of HTLV-1 PR (3WSJ)

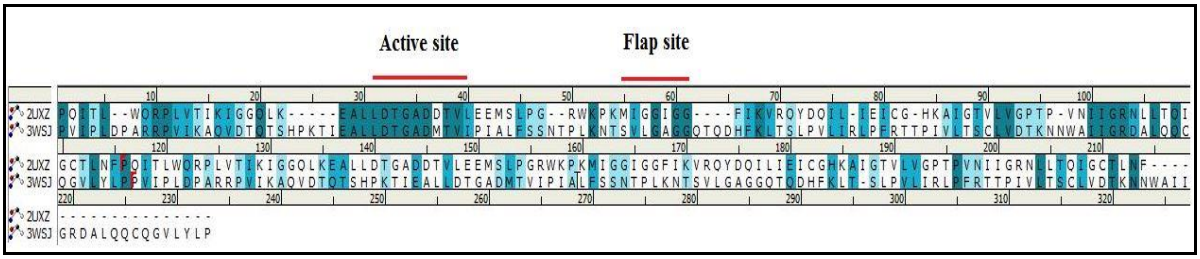


Fig. 1b. Alignment of HTLV-1 PR vs HIV-1 PR amino acid sequences

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The Indinavir-HTLV-1 PR complex crystallography indicates the hydrophobic bonds of drug to residues in S1, S2-S4, S1', and S2'-S4' pockets. In addition, HTLV-1 PR through its own Gly34, can make a hydrogenous bond to the Indinavir. With regards to assessment of interactions between Indinavir and the HTLV-1 protease's main functional pockets, it appears that, with induction of changes in Indinavir structure, for reinforcement of interactions between drug and functional pockets of viral protease, better candidates can be designed for inhibition of HTLV-1 PR [16].

Therefore, in the next step, in order to improvement of drug against HTLV-1 PR, ΔG of Indinavir and HTLV-1 PR was estimated -172.235 Kcal/mol. Then using docking results of Indinavir four combinations were designed, which named KMI (Keikha Modified Indinavir) 1-4. Some properties of these candidates are listed in Table 1.

Table 1. The list of properties of different drugs (or drug candidates) against HTLV-1 PR

Drug name	Docking energy	Hydrogenous bonding agent	Hydrogen bonding receptor	Length bond
Indinavir	-172.235	O17 O65	Ala59 Asp32	-2.7 -3.1
KMI-1	-189.796	N1 O21 O43	Arg10 Asp32 Leu57	-3.3 -2.5,-3,-3.2 -2.4
KMI-2	-176.97	N31 O43	Gly34 Met37	-3 -2.4,-1.2
KMI-3	-220.411	O42 N1 O31 O20	Leu57 Ala59 Met37 Gly34,Asp36	-2.5 -1,-1.4 -2.4 -2.5,-0.5
KMI-4	-189.919	O14 O31 O75 O20 O42	Ala59 Ala59 Ala99 Asp32 Gly34	-0.3 -0.5 -1.2 -2.5,-0.1,-2.5 -0.8

Given that pharmacophores KMI 1-4 were modeled based on fragment-based design of HTLV-1 PR, so it was expected that, new designed compounds would have higher interaction and docking energy than Indinavir (Figure 3). The results confirmed this hypothesis; for example, about the KMI-3, hydrophobic and hydrogenous interactions was increased significantly, and effectively occupied S1/S1', S2/S2', S3/S3' and S4/S4'.

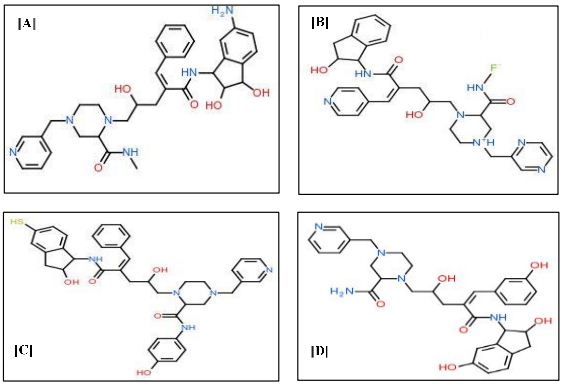


Fig. 3. Formula of four different pharmacophores. (A) Pharmacophore KMI 1; (B) Pharmacophore KMI2; (C) Pharmacophore KMI3; Pharmacophor KMI4.

As respects Met37 plays an obvious role in the inactivity of anti-HTLV- PR drugs, especially Indinavir; therefore, new compounds (e.g. KMI-3) were designed in a way that elicits a particular interaction with this amino acid (Figure 4).

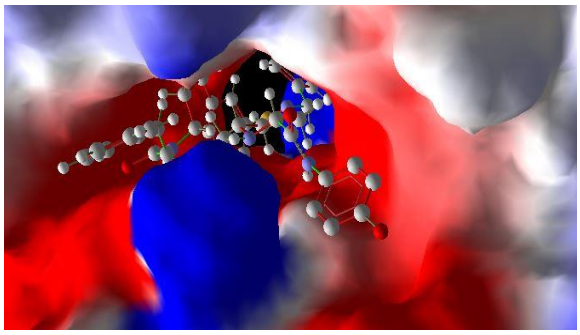


Fig. 4. Positioning of KMI-3 in HTLV-1 PR avtive site. The size and functional groups of this compound are designed based on drug-binding pockets, so that KMI-3 is exactly fitted in the enzyme's active site space.

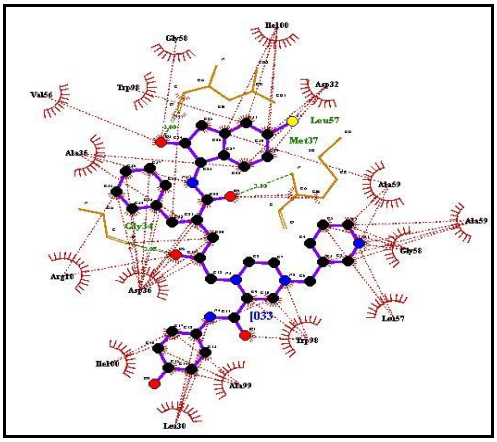


Fig. 5a. Hydrogenous and hydrophobic interactions between KMI-3 and HTLV-1 PR based on LigPlot+ program.

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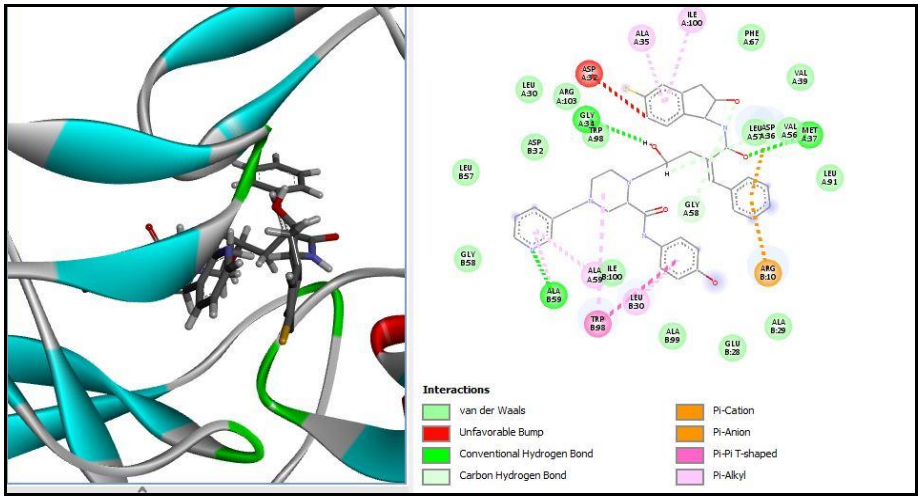


Fig. 5b. Hydrogenous and hydrophobic interactions between KMI-3 and HTLV-1 PR based on Discovery studio program.

Table 2. Docking information of Indinavir compared to four KMIs

	Drug likeness score	1.8	1.6	2.0	1.7	2.38
	Swiss target prediction	Protease	Protease	Protease	Protease	Protease
	Mutagenicity	0.0814	0.108	0.018	0.0813	0.0381
	Carcinogenicity (Mouse)	0.108	0.1		0.0808	0.0458
	Carcinogenicity (Rat)	0.0888	0.0936		0.082	0.0628
	Mol-LogS	-3.68	-2.77	-2.11	-5.51	-2.57
	Number of HBA	7	8	8	9	9
	Bioavailability Score	0.55	0.17	0.17	0.55	0.17
	BBB permeant	Yes	Yes	Yes	Yes	Yes
	BBB permeant	No	No	No	No	No
	Water Solubility	Moderately soluble	Soluble	Soluble	Soluble	Moderately soluble
	Log Po/w	3.95	2.96	0.00	3.29	3.22
	TPSA	118.03 Å²	164.28 Å²	145.01 Å²	177.06 Å²	172.48 Å²
	Molecular weight	613.79 g/mol	600.71 g/mol	591.68 g/mol	679.83 g/mol	587.67 g/mol
	Formula	$C_{36}H_{47}N_5O_4$	$C_{33}H_{40}N_6O_5$	$C_{31}H_{38}FN_7O_4$	$C_{38}H_{41}N_5O_5S$	$C_{32}H_{37}N_5O_6$
	Drug name	Indinavir	KMI-1	KMI-2	KMI-3	KMI-4

Discussion

Due to 3D structure similarities of HTLV-1 and HIV-1 proteases, first it was thought that, HIV-1 PR inhibitors be able to inhibit the HTLV-1 protease, too. Dewan et al. they showed that HIV-1 proteases such as KNI-727, KNI-764, and Ritonavir, are not completely be able to inhibit HTLV-1 protease [16-17]. Recently, Kuhnert et al, published the HTLV-1 PR-Indinavir complex structure (3 SWL). More evaluation showed that, each of HTLV-1 and HIV-1 proteases chain have owned 116 and 99 amino acids residues, respectively. HTLV-1 PR have distinctive and impressive properties, which have distinguished it from HIV-1 PR. Those include Met37 in active site (instead Asp60 in HIV-1 PR), Leu57, Asn97, Trp98 in S3/S3' binding pocket (Arg10, Leu30, and Asp36 are common); as well as Loop 97-97 (including Asn97 and Trp98), in S3 pocket, which is accounted as main factor responsible for rejection of anti-HIV-1 PR drugs [16-19]. In addition, both enzymes have three binding domains, including active site, flag region, and C-terminal region; bonding of different compounds to these domains causes substantial changes in 3D enzyme conformation, and lead to its activity or inhibition. So, for construction of specific HTLV-1 PR inhibitors, more studies are required [6,20]. In the present study, first, HTLV-1 PR-Indinavir

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crystallography complex was evaluated, and then drug orientation into the HTLV-1 PR binding pocket was confirmed. Next, using Molegro virtual docker software, drug bonding energy to HTLV-1 PR was assessed; the energy of closest orientation towards crystallography structure was equivalent of -172.23 KJ/mol-1. Then, considering the electrical charge, H-bond capacity, and HTLV-1 PR hydrophobic binding pocket, some pharmacophor were recommended, and their pharmacologic criteria including lack of toxicity for humans, solubility, low mutagenicity, specificity (protease targeting) were confirmed by online data bases such Swiss ADME, LAZAR, and Molinispiration. The docking information of these compounds showed better results than Indinavir (Table 2).

However, KMI-3 (Keikha modified indinvir-3) with -220.41 KJ/mol-1 energy, had highest capacity for induction of hydrogenous and hydrophobic bonds (Figure 5a-b and Table 2). Based on studies, Met37 is located in the outermost part of binding pocket S4, and is accounted as the main factor for rejection of anti-HIV-1 proteases in HTLV-1 virus.

Selvaraj et al. demonstrated that none of each anti-HIV-1 protease inhibitors cannot interaction with Met37 in HTLV-1 PR structure.

Nonetheless, in present study, KMI-2 and KMI-3 can produce a relatively strong hydrogenous bond with this amino acid [13,18].

Also, KMI-1 can make hydrogeneous bond with Asp32 and Leu57; the S3-S3' part has assigned to itself a large volume of HTLV-1 PR binding pocket, so that bond to and inhibition of these residues (Asp32 and Leu57), has important role in the inhibition of HTLV-1 protease enzyme [13,19]. Based on Li et al. studies, Leu57 and Trp98 in binding pocket S3/S3', play a pivotal role in difference between HTLV-1 and HIV-1 protease.

The presence of these amino acids increase in S3/S3' pocket leads to hydrophobicity of pocket, cover of Asn97, and eventually decrease in bond of drug to enzyme [21].

Accordingly, KMI-3 and KMI-4 were designed in a way that cause a hydrophobic bond with Trp98; so are able to block the rejection effect of Trp98 of HTLV-1 PR. Selvaraj et al. proved that apart from similarities between both active sites, the size of binding pockets of enzymes are different with each. The binding pocket in HTLV-1 protease is Z form, and its most important amino acids include Arg10, Leu30, Asp32, Gly34, Ala35, Asp36, Met37, Val39, Leu57, Ala59, Leu91, Trp98, and Lle100 [13,22]. Overall, several studies showed that, by creating partial structural changes, anti-HIV-1 PR drugs such as Tipranavir, Indinavir, Darunavir and Amprenavir, can inhibit effectively HTLV-1 PR [13,23].

So far, numerous anti-HTLV-1 PR compounds such as peptido-mimetics (peptoids, peptido-sulfanomids), statine based inhibitors, HIV-1 Protease inhibitors, MES13-099, JG-365, and etc. have synthesized and studied. However, each one has some disadvantages; for example, statin compounds are only active in micromole concentrations; as well reduction in solubility and bioavailability of peptidomimetics, and insufficient specificity of MES13-099 [6, 18, 23-24]. As a rule of thumb, with a little change in the structure of FDA approved anti-HIV-1 proteases, they exchange to specific anti-HTLV-1 protease [13, 24].

Conclusion

In summary, in the present research, first, HIV-1 and HTLV-1 sequences was compared with each other, and unique regions in HTLV-1 protease were identified. In the next step, modified pharmacophores based on Indinavir were constructed, which include better molecular docking outputs. It seems modification of anti-HIV-1 proteases is the best strategies for development of specific anti-HTLV-1 proteases, and probably will be proved in the future in vitro studies.

Conflict of Interests

None to declared.

Ethical Considerations

The Ethics Committee of Mashhad University of Medical Sciences was approved the study.

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