

Peptidomimetics Based Inhibitor Design for HIV – 1 gp120 Attachment Protein

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Abstract

Peptidomimetics is a novel drug designing strategy in which an *In silico* inhibitor is designed by mimicking the framework of a short peptide. Novel drug design strategies shall only pave way for developing unique and safer anti-HIV drugs. In the present study, we propose a Peptidomimetics based gp120 attachment inhibitor. In human biological system, HIV-1 interacts with CD4 receptor of the host via its surface glycoprotein gp120 establishing initial attachment. This protein–protein interaction interface forms the base to derive an inhibitor mimicking backbone of the receptor. The mimicked inhibitor derived in this study is based on the *in silico* interactions of soluble CD4 (SCD4) (precursor of CD4) with gp120. The molecular interactions of SCD4 with gp120 were identified by MEdock software. Furthermore, the interacting interface was analyzed manually for topology, and the backbone of the ligand molecule was sketched based on it with chemsketch. Moreover, the sketched ligand was optimized and was docked with gp120 using Argus lab. Docking results show six hydrogen bonds formation between the ligand and binding interface of gp120. The ligand was also found to be fit with good druggable character, as per Lipinski's rule of five. Hence, this work addresses the drug likeness of the peptidomimetic ligand proposed.

Keywords: Peptidomimetics; HIV-I gp120; CD4; SCD4; Arguslab; MEdock

Introduction

HIV – 1 multiplies only inside human cells. They invade the host's immune system after attaching to a special protein called CD4, which spans on host cell's surface. HIV- 1's surface molecule gp120 plays a crucial role in host infection, since it mediates attachment of virus to its target cells (Wyatt and Sodroski, 1998). The prime objective of the present study was to uncover a solution to inhibit this attachment via a novel peptidomimetic inhibitor. The discussed inhibitor is based on CD4 receptor region for gp120.

Gp120 (PDB ID: 1CE4) trimer with a Molecular weight of 120KDa is a glycoprotein present on the surface of HIV envelope. This glycoprotein comprises of five variable loop regions namely, V1, V2, V3, V4, and V5. The V3 loop region particularly interacts with first domain of CD4 protein with high affinity due to favourable amino acid interactions. The structure of V3 region of HIV gp120 was determined using NMR in 1999.

This region is proven to be immunodominant and is composed of 35 amino acids (Kwong et al., 1998; Vranken et al., 2001; Lasky et al., 1987; Berger and Alkhatib, 2007) .

Soluble CD4 (SCD4) is the precursor of CD4. Normally SCD4 induces conformational changes in gp120 synonymous to that of CD4 (Turner et al., 1992). The sub domain region of SCD4 N-termini (PDB ID: 1CDH) was proven to have high interaction towards gp120 than CD4. Hence, for the present study, SCD4's sub domain region was utilized for peptidomimetic modeling. SCD4 was sequenced in the year 1986 and structure was elucidated by X-ray diffraction (Ryu et al., 1994).

The effective way to predict binding affinity of macromolecular structures is by docking simulation. Moreover, docking studies pave way for studying the interacting interfaces and their topology. Hence, in the present work SCD4 peptide's sub-domain was docked with gp120 using MEdock software (<http://bioinfo.mc.ntu.edu.tw/medock/>). The interacting interface was scanned for residues conferring binding topology, which was in turn used to derive a chemical backbone mimicking the binding topology of SCD4 subdomain. Hence, implementing peptidomimetic approach, the chemical backbone structure was sketched and 3D optimized using Chemsketch. Finally, the sketched ligand was docked with gp120 using Arguslab (www.arguslab.com). It qualified in Lipinski drug calculator (<http://www.scfbio-iitd.res.in/utility/LipinskiFilters.jsp>).

Methods

Preparation of Target Protein Structure

Protein Data Bank (PDB) is a repository of 3-D structural data of bio macromolecules (<http://www.rcsb.org/pdb/>). In the present study, the atomic coordinates of the HIV-V3 loop of the envelope glycoprotein gp120 (1CE4) was procured from the Protein Data Bank (PDB) (Vranken et al., 2001). It contains 35 amino acids with a disulphide bond. It forms 3 helices, 5 beta turn and 1 gamma turn (Vranken et al., 2001). The atomic coordinates were processed using Swiss PDB Viewer, a user friendly

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Received October 29, 2009; **Accepted** November 25, 2009; **Published** November 25, 2009

Citation: Vetrivel U, Sankar P, Nagarajan NK, Subramanian G (2009) Peptidomimetics Based Inhibitor Design for HIV – 1 gp120 Attachment Protein. J Proteomics Bioinform 2: 481-484. doi:10.4172/jpb.1000109

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tool to analyze protein structures (<http://spdbv.vital-it.ch/>) (Figure 1).

Preparation of Ligand Through Peptidomimetics

The coordinates of SCD4 (1CDH) subdomain region was restricted using Rasmol, an interactive Molecular visualization and editing tool (www.umass.edu/microbio/rasmol/). (Figure 2). The restricted domain was docked with gp120 using MEdock, an online tool to predict ligand-binding interactions (<http://bioinfo.mc.ntu.edu.tw/medock/>). Binding interactions between SCD4 domain and gp120 were identified by MEdock. Five residues namely, Aspartate 10, Threonine 11, Valine12, Glutamate 13, and Leucine 14 of SCD4 showed significant interaction with Gp120. These five residues were restricted and extracted using Rasmol and were again docked with gp120 using MEdock. The best binding pose as per MEdock's first rank was utilized for peptidomimetic study. Four hydrogen bonds were formed by Valine 12, Glutamate 13, Leucine 14 of SCD4 with that of Gp120. The Hydrogen bonds were visualized using Pymol, a python based molecular visualization tool used to produce publication quality images (www.pymol.org) (Figure 3).

Peptidomimetic ligand was sketched based on the interactive

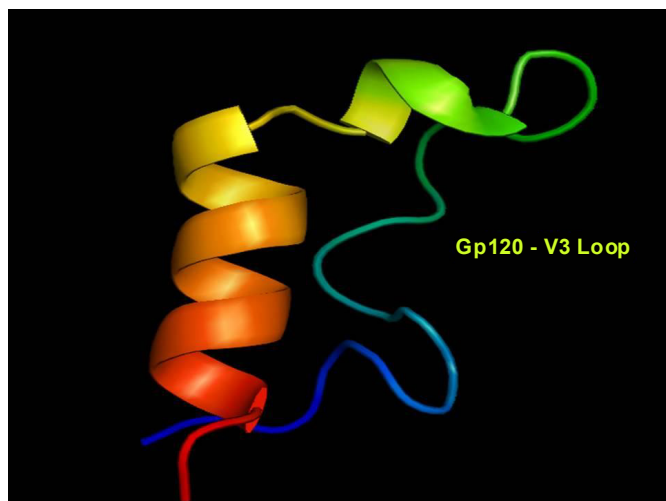


Figure 1: Three Dimensional Structure of gp120 V3- Loop.

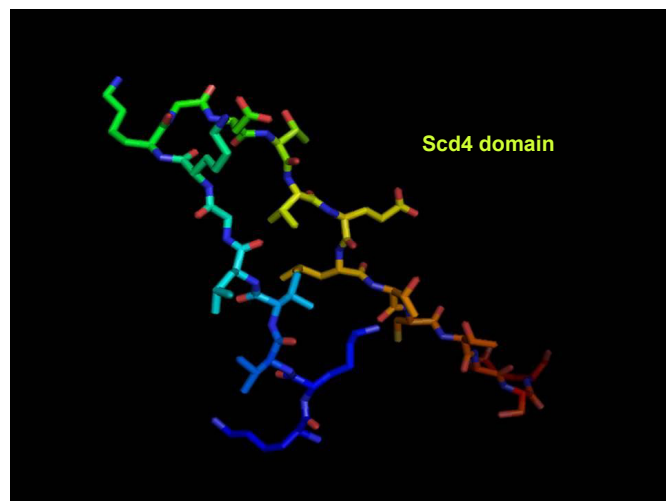


Figure 2: Showing the Domain region in Soluble CD4 (1-20 residues).

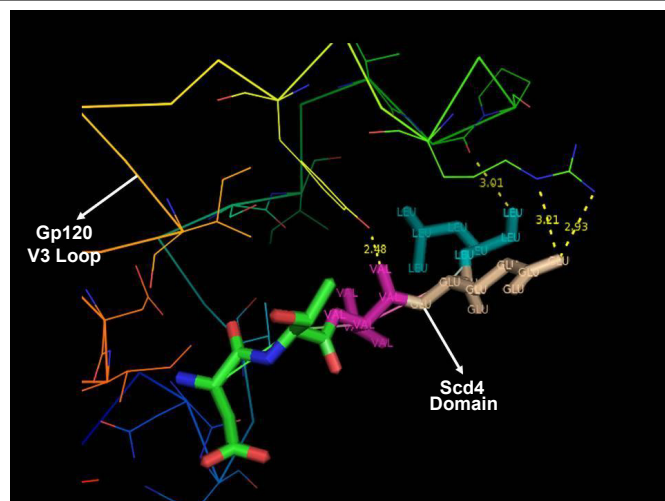


Figure 3: Showing docked structure of SCD4 Interactive domain region with gp120. (The yellow lines (discontinuous) show the hydrogen bonds formed between gp120 and interactive region of SCD4).

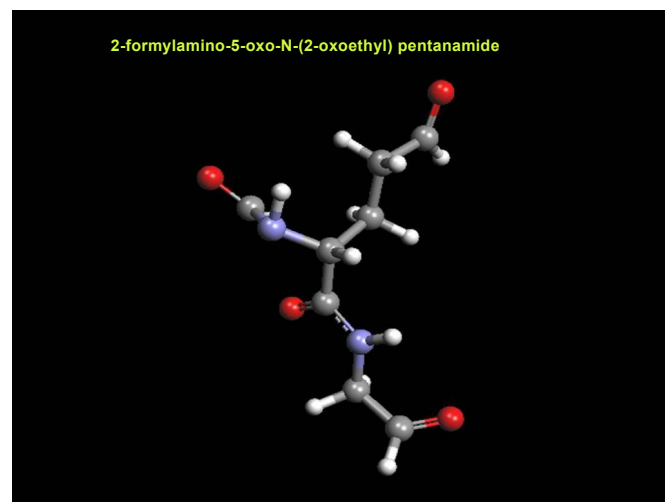


Figure 4: The peptidomimetic ligand 2-formylamino-5-oxo-N-(2-oxoethyl) pentanamide contains 26 atoms sketched based upon the hydrogen bonding pattern between gp120 and interactive residues in SCD4.

binding interface of gp120 and SCD4. The scaffold of hydrogen bonding residues of SCD4 (VAL-12, GLU -13, LEU- 14.) was taken as the backbone to sketch the peptidomimetic ligand namely, 2-formylamino-5-oxo-N-(2-oxoethyl)pentanamide employing Chems sketch, a freeware for chemical structure drawing and optimization from ACD Labs. This software also enables conversion of drawn 2D to 3D structure and subsequent Optimization, and was utilized for the same in this study (Figure 4) (www.acdlabs.com/download/).

Protein –ligand Docking

Docking of the receptor with the ligand was performed using Argus lab which operates on Lamarckian genetic algorithm (www.arguslab.com). Both the receptor and ligand were optimized for proper geometry using Argus lab, prior to docking. Finally, the best ligand pose was found to be with lowest binding energy of -6.86617 kcal/mol. The obtained complex showed

six hydrogen bonds within the range of 3 Angstrom distance (Figure 5, Figure 6) (Table 1).

Lipinski 5 Screening

This screening methodology was implemented to analyze the Drug likeness of the proposed ligand. Lipinski's rule of 5 is an essential screening methodology for rational drug design (Ekins and Rose, 2002; Miteva et al., 2006; Smith et al., 2004). It states that poor absorption or permeation are more likely when a ligand molecule violates Lipinski's rule of five i.e., has more than 5 hydrogen bond donors, the molecular weight is over 500, the log P is over 5 and the sum of N and O is over 10. The Ligand of the present study has well qualified in Lipinski's filter (<http://www.scfbio-itt.res.in/utility/LipinskiFilters.jsp>) (Table 2).

Results and Discussion

HIV-1's gp120 V3 region has high affinity towards SCD4 receptor [3]. The present study was initiated to explore the possibility to develop an inhibitor mimicking the above mentioned interaction. Hence, Peptidomimetics approach was implemented

GP120		Inhibitor	Distance
Residue	Atom		
Arg 9	O	H(25)	2.64A°
Ile 12	NH	O(12),O(14)	2.81A°,2.76A°
His 13	NH	O(14),O(12)	2.60A°,2.89A°
Glu 25	OH	O(11)	2.69A°

Table 1: Showing the Hydrogen Bonding details between GP120 and the Inhibitor.

Lipinski's Rule of 5	
Molecular Weight	200
Hydrogen Acceptors	4
Hydrogen Donors	2
LogP	-1.596

Table 2: Showing the Lipinski's Value for the peptidomimetic ligand.

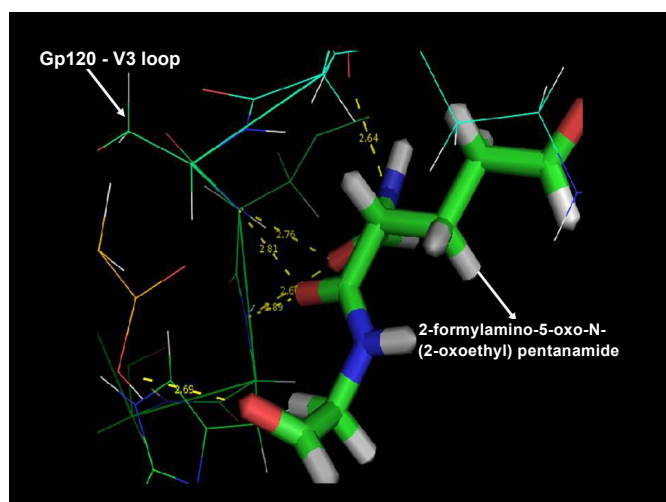


Figure 5: Peptidomimetic ligand docked with gp120. (The yellow lines (discontinuous) represent the hydrogen bonds. Six hydrogen bonds were seen ranging within 3A°).

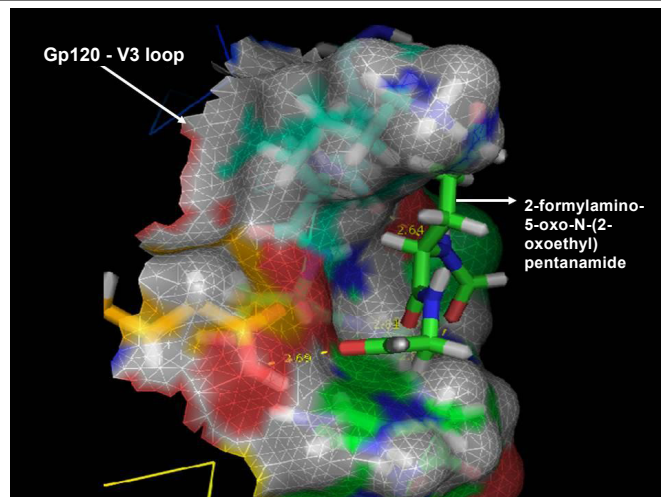


Figure 6: Showing Peptidomimetic ligand (2-formylamino-5-oxo-N-(2-oxoethyl) pentanamide) bound perfectly within gp120 binding pocket.

to develop the inhibitor. The derived peptidomimetic inhibitor was docked with gp120 V3 region and was found to have significant affinity (Table 1) (Figure 5, Figure 6). We also screened the docked ligand for Lipinski's rule of 5, which in turn proved to be a qualified drug (Table 2).

Entry inhibitors represent a new generation of antivirals for the treatment of HIV infection. Several compounds blocking the attachment of HIV gp120 to either the CD4 T cell receptor or the CCR5/CXCR4 co-receptors are currently in clinical development. Most of these compounds have different molecular structures and possess specific mode of action. These agents are eagerly awaited by a growing number of patients. Enfuvirtide is the first and the only clinically approved entry inhibitor for HIV, and it blocks HR1, HR2 zipping process in fusion step. So far three attachment inhibitors are designed namely, BMS-806, PRO 542, and TNX-355. These inhibitors are designed based on the existing drugs (Briz et al., 2006; Madani et al., 2006; Moore and Stevenson, 2000). Whereas, the drug designed in the present study is unique and is based on the gp120's interaction with SCD4.

Conclusion

SCD4 has been found to prevent HIV attachment to cells in experiments, by the simple process of HIV's envelope protein "spikes" attaching to it and thus being unable to attach to ordinary CD4 protein (Turner, 1992; Moore and Stevenson, 2000; O'Hara and Oslon, 2002; Layne et al., 1990). At low SCD4 concentration, the inhibition of HIV infection is proportional to the binding of gp120 with SCD4 (Layne et al., 1990). We propose that the drug designed in the present study might be more effective since it mimics the SCD4 interaction, as it also forms significant hydrogen bonds and qualifies in Lipinski's filter. Hence, the proposed drug is presented to the scientific community for further experimental validation.

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