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Exploration of the Binding Mode of Indole Derivatives as Potent HIV-1 Inhibitors Using Molecular Docking Simulations

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Abstract

The HIV-1 envelope glycoprotein gp120 plays a vital role in the entry of the virus into the host cells. The crucial role of the glycoprotein suggests gp120 as potential drug target for the future antiviral therapies. Identification of the binding mode of small drug like compounds has been an important goal in drug design. In the current study we attempt to propose binding mode of indole derivatives in the binding pocket of gp120. These derivatives are reported to inhibit HIV-1 by acting as attachment inhibitors that bind to gp120 and prevent the gp120-CD4 interaction and thus inhibit the infectivity of HIV-1. To elucidate the molecular basis of the small molecules interactions to inhibit the glycoprotein function we employed the molecular docking simulation approach. This study provides insights to elucidate the binding pattern of indole-based gp120 inhibitors and may help in the rational design of novel HIV-1 inhibitors with improved potency.

Key words: HIV-1, gp120, Indole Derivatives, Docking

1. Introduction

Human immunodeficiency virus (HIV) is the etiologic agent of acquired immune deficiency syndrome (AIDS) that has emerged as one of the most devastating infectious diseases in the recent history. The HIV-1 entry into the host cells is a multi-step process. The process includes the sequential interaction of the viral envelope glycoprotein, gp120 with the CD4 glycoprotein and CCR5 or CXCR4 chemokine receptors present on the cell surface. These interactions induce fusion of the viral and cellular membranes and viral core entry into the host cell cytoplasm[1-3]. Every step in the overall process provides potential targets for drug discovery[4]. Entry inhibitors represent an emerging class of antiretroviral agents which block viral entry into the cells. Previous studies have reported several indole-containing molecules that hinder the attachment of gp120 to CD4 by binding to the CD4 binding site in gp120[5,6]. Compound 2 (Fig. 1a) is reported as a small indole-based HIV-1 attachment inhibitor (EC_{50} =1.24 nM) that effectively blocks the binding of CD4 with gp120. During the optimization process of the early lead compound; the C-7-tetrazole analog 3 (Fig. 1b) demonstrated improved antiviral potency (EC_{50} = 0.034 nM)[7]. Binding mode of both the inhibitors remains unknown.

Our computational research group is actively involved in the molecular modeling studies of small molecules and proteins. Previously, this group has reported several papers covering different applications[8-12]. In order to

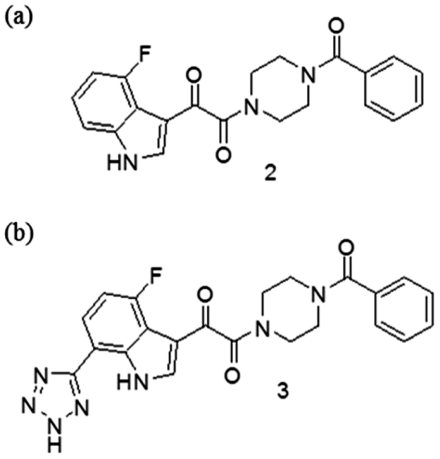

Fig. 1. HIV-1 attachment inhibitors: (a) lead compound 2 and (b) the C7-tetrazole analog 3.

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investigate the importance of the tetrazole group at the 7-position of the indole ring and to predict the binding mode of these inhibitors in the binding pocket of gp120; molecular docking simulations were performed. The binding models were demonstrated in the aspects of inhibitor's conformation, subsite interaction and hydrogen bonding. The findings of this study suggest useful insights regarding possible binding mode of this kind of inhibitors. This study further provides useful information for future rational design of novel and more potent HIV-1 inhibitors.

2. Experimental Section

2.1. Preparing Small Molecules

Indole derivatives were sketched and 3D structures were optimized by Sybyl8.1 and saved in Protein Data Bank (PDB) file format. These small molecules were prepared for molecular docking by merging non-polar hydrogens, assigning Gasteiger charges, defining the rotatable bonds, assigning AutoDock type to each atom and saving them in PDBQT file format using AutoDock Tools (ADT) 1.5.6.

2.2. Preparing Target Molecule

Till date, no crystal structure of gp120 in complex with indole derivatives has been reported. For the present study, a recent X-ray crystal structure of gp120 (PDB code: 4DKR, 1.8 Å resolution) was retrieved from RCSB protein databank (http://www.rcsb.org/pdb). During the protein preparation all the heteroatoms including co-crystallized ligand as well as water molecules and ions were removed from the receptor using PyMOL v0.99. Polar hydrogen atoms were added and Gasteiger charges were assigned to the target protein structure and finally macromolecule was saved in PDBQT file format using ADT. The resulting target protein structure was used in molecular docking studies.

2.3. Molecular Docking

Molecular docking simulations were carried out with the AutoDock 4.2.5.1[13] considering all the rotatable bonds of small molecules as rotatable and macromolecule as rigid. AutoGrid calculations were used to define the search grid and grid maps. A grid box of 40×40×40 Å dimension with 0.375 Å spacing was created and centered on the active site residue Trp427 of the macromolecule. The docking parameter file with the instructions about the ligand to move, the map files to use and other properties to use was created using ADT. Grid and docking parameter files were used later by AutoDock for running the docking simulations. Lamarckian Genetic Algorithm (LGA) with default parameters was employed to perform molecular docking. Hundred independent docking runs were performed for both small molecule and 2,500,000 energy evaluations were applied for each run. Lowest energy conformation of each small molecule was considered as active conformation among all the observed conformations and selected for analysis. From the several docked poses, the protein–small molecule complex formed with least energy and with a stable conformation from the largest cluster was saved in PDBQT format and then converted to PDB file format using Python Molecular Viewer (PMV) 1.5.6. Docking results were analyzed using PyMOL and LigPlot. Docking studies were performed on PC with Microsoft Windows 7 Home Premium version 2009, Intel(R) Core(TM)i5CPU (3.10 GHz) operating system.

3. Results and Discussion

Docking studies were performed to gain insights into the most probable binding mode of the indole-containing inhibitors. Docked pose of both the compounds were selected on the basis of the docking score and interactions with the active site residues. Hydrophobic interactions of the docked compounds were calculated using the LIGPLOT server (http://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/). Docking analysis revealed that indole ring was placed deep into the gp120 cavity enclosed by hydrophobic residues whereas the piperazine ring of was docked at the entrance of gp120 binding pocket lined by Ile371, Ile424, Asn425, Met426, Trp427 and Ile475 residues. The hydrophobic site was composed of the Thr257, Ser375, Phe382, and Trp427 residues. This observation was in accordance with the experimental mutational study[14].

In addition, tetrazole substituted analogue 3 was inserted deep inside the pocket lined by the Val255, Ser256, Thr257, Ser375, Phe376 and Asn377 residues. Also, NH of the tetrazole ring established hydrogen bond interaction with main chain carbonyl of Val255, which appears to be important for biological activity.

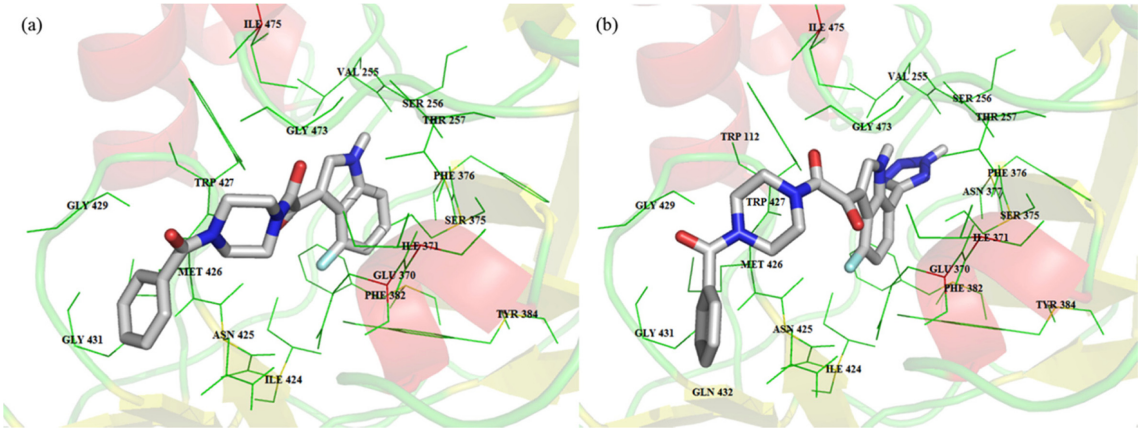

Fig. 2. Binding mode of compound 2(a), compound 3(b) and gp120 extracted from the docking results. In panels (a) and (b), the protein is represented by the solid ribbon model and colored by the secondary structures. The compounds are represented by a cap-and-stick model and colored by elements. The side chains of some key residues are lined out.

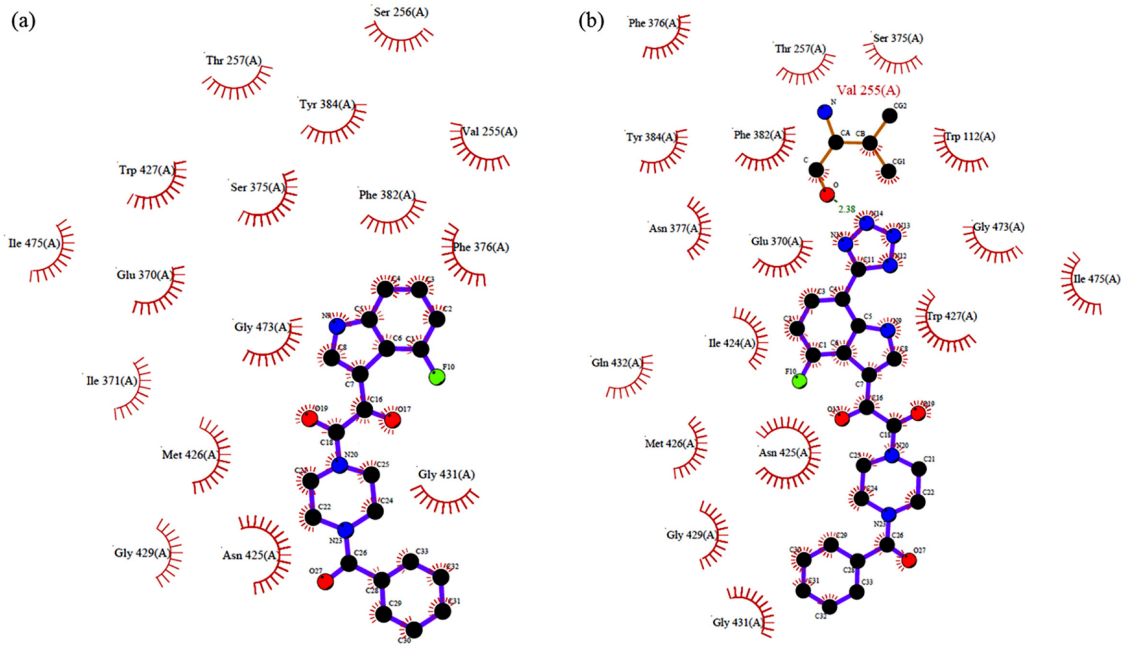

Fig. 3. Two-dimensional scheme of interactions between the compound 2(a), compound 3(b) and gp120 generated by LIGPLOT. Only the more important residues for binding are shown after docking. Brown stick models present the important residues in the active site, thick purple stick models present the inhibitor, green dotted lines are hydrogen bonds and dashed half-moons present hydrophobic interactions with the corresponding amino acid residues of gp120.

Tetrazole ring was oriented in such a way that it could minimize steric interactions with indole ring and form hydrogen bond with surrounding residue. However, unsubstituted analogue 2 showed comparatively less interactions in the binding pocket and exhibited only hydrophobic interactions. Closer hydrophobic interactions were observed for compound 3 with Trp112, Thr257, Glu370, Ser375, Phe376 and Asn377. Probably, substitution on indole at 7-position could be the determining factor for improving inhibitory activity.

The binding modes of the compounds and their hydrophobic interactions with the active site residues are shown in Fig. 2 and 3, respectively. Binding modes of the compounds in the binding pocket of gp120 are in agreement with the reported studies[15,16].

4. Conclusions

The present computational study provides insights into the potential binding site and binding mode of indole-based gp120 inhibitors. The docking results identified the important residues in gp120 for interactions. Careful analysis of the docking results shows that the indole ring of the inhibitors inserts deep into the binding pocket and piperazine ring fits at the entrance of binding site. Also, tetrazole substituted compound 3 docks deep into the crevices of target protein and shows better hydrophobic and hydrophilic interactions as compared to the unsubstituted compound 2, which shows only hydrophobic interactions. This may be the reason why former shows more activity. We can also conclude that residues Trp112, Val255, Ser375, Glu370, Asn425, Trp427 and Gly473 play an important role in the binding of indole based inhibitors.

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