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Computational Analysis of Drug Design HIV-1 Integrase Target Protein

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ABSTRACT

Background: HIV-1 (Human Immuno Deficiency Virus) attacks the immune system and cannot treat which leads to AIDS (Acquired Immuno Deficiency Syndrome). HIV-1 integrates (IN) is a transfer inhibitor retroviral enzyme essential for the integration of genetic material into the DNA of the host cell and hence for viral replication. The absence of an equivalent enzyme in humans makes it an interesting target for anti-HIV drug design. **Methods:** The research aims to analyze the binding modes of SWISS-MODEL, H-DOCK, 3D-LIGAND SITE, and COMPUTATIONAL TOOLS. Swiss-model is a structural bioinformatics webserver dedicated to homology modeling 3D-protein structure. Docking computational simulation of a candidate ligand binding to a receptor is the process of classifying which ligands are mostly likely to interact favorably with a particular receptor based on the predicted free energy of binding. Docking assessment procedure to quantify the predictive capability of a docking protocol. **Result:** In biochemistry and molecular biology a binding site is a region of a macromolecule such as a protein that binds to another molecule with specificity. The binding partner of the macromolecule is often referred to as a ligand. This technology was using the further advances of drugs against Human Immuno Deficiency Virus-1. **Conclusion:** These results elucidate the basis for the inhibition of strand transfer and imply integrase-directed HIV-1 drug discovery efforts. Despite the availability of 25 anti-AIDS medications that have been licensed, there is still a need for the development of new therapies to treat AIDS for a variety of reasons, with the main one being the need for better resistance profiles.

INTRODUCTION

Human Immunodeficiency Virus type 1 (HIV-1) is characterized by vast genetic diversity. Globally circulating HIV-1 viruses are classified into distinct phylogenetic strains (subtypes, sub-subtypes) and several recombinant forms [1]. Here we describe the characteristics and evolution of the European HIV-1 epidemic over time through a review of published literature and updated queries of existing HIV-1 sequence databases. HIV-1 in Western and Central Europe was introduced in the early-1980s in the form of subtype B, which is still the predominant clade. However, in Eastern Europe (Former Soviet Union (FSU) countries and Russia) the predominant strain, introduced into Ukraine in the mid-1990s, is subtyping A (A_{FSU}) with transmission mostly occurring in People Who Inject Drugs (PWID). In recent years, the epidemic is evolving towards a complex tapestry with an increase in the prevalence of non-B subtypes and recombinants in Western and Central Europe [2]. Non-B epidemics are mainly associated with immigrants, heterosexuals, and females but more recently, non-B clades have also spread amongst groups where non-B strains were previously absent - non-immigrant European populations and amongst men having sex with men (MSM). In some countries, non-B clades have spread amongst the native population, for example, subtype G in Portugal and subtype A in Greece, Albania, and Cyprus. Romania provides a unique case where sub-subtype F1 has predominated throughout the epidemic [3]. In contrast, the HIV-1 epidemic in FSU countries remains more homogeneous with the A_{FSU} clade predominating in all countries. The differences between the evolution of the Western epidemic and the Eastern epidemic may be attributable to differences in transmission risk behaviors, lifestyle, and the patterns of human mobility. The study of HIV-1 epidemic diversity provides a useful tool by which we can understand the history of the pandemic in addition to allowing us to monitor the spread and growth of the epidemic over time [4].

HIV-1 integrase (IN) is a retroviral enzyme essential for the integration of genetic material into the DNA of the host cell and hence for viral replication. The absence of an equivalent enzyme in humans makes IN an interesting target for anti-HIV drug design. This review briefly overviews the structural and functional properties of HIV-1 IN. We analyze the binding modes of the established drugs, clinical candidates, and a comprehensive library of leads based on innovative chemical scaffolds of HIV-1 IN strand transfer inhibitors (INSTIs) [5,6]. Computational clustering techniques are applied for identifying structural features relating to bioactivity. From bio- and chemo-informatics analyses, we provide novel insights into structure–the activity relationships of INSTIs and elaborate new strategies for the design

of innovative inhibitors [5]. Human immunodeficiency syndrome (HIV-1) has infected over 75 million people and over 35 million have succumbed to virus-related illnesses. Despite access to a variety of antiretroviral therapy (ART) options, ART programs have been disproportionally spread in the world with low-and middle-income countries (LMICs) facing challenges to access the most potent ART options [7]. With less potent ART remaining in use in LMICs, HIV-1 drug resistance (HIVDR) presents a growing challenge in LMICs. Since the approval of the first-generation integrase strand transfer inhibitor (INSTI), Raltegravir (RAL) in 2007, INSTIs remain the best choice as a backbone of ART.

Mechanism- Integration of retroviral DNA is an obligatory step of retrovirus replication because pro-viral DNA is the template for productive infection. Integrase, a retroviral enzyme, catalyzes integration. The process of integration can be divided into two sequential reactions. The first one, named 3'-processing, corresponds to a specific endonucleolytic reaction that prepares the viral DNA extremities to be competent for the subsequent covalent insertion, named strand transfer, into the host cell genome by a trans-esterification reaction [8]. Recently, a novel specific activity of the full-length integrase was reported, *in vitro*, by our group for two retroviral integrases (HIV-1 and PFV-1). This activity of internal cleavage occurs at a specific palindromic sequence mimicking the LTR-LTR junction described in the 2-LTR circles which are peculiar viral DNA forms found during viral infection. Moreover, recent studies demonstrated the existence of a weak palindromic consensus found at the integration sites [9]. Taken together, these data underline the propensity of retroviral integrases for binding symmetrical sequences and give perspectives for targeting specific sequences used for gene therapy.

Integrase- Integrase is a 288 amino acid protein (32 kDa) encoded by the end of the *pol* gene. It is produced as part of the Gag-Pol polypeptide precursor, from which it is released by viral protease-mediated cleavage. It has three independent domains: (i) The N-terminal domain (amino acids 1–49) that carries an HHCC motif analogous to a zinc finger, and effectively binds Zn^{2+}, possibly favoring protein multimerization, a key process in integration. (ii) The central domain or catalytic domain (amino acids 50–212) encompassing a D, D-35, E motif which is indispensable for the catalytic activity and which is conserved between viral IN and transposases [10]. This central domain is also implicated in the binding of the viral DNA extremities mainly via the residues Q148, K156, and K159. All integrase activities strictly require the presence of a metallic cationic cofactor which is coordinated by two residues of the catalytic triad (D64 and D116 for HIV-1 IN). (iii) The C-terminal domain

(amino acids 213–288) binds non-specifically to DNA and therefore is mainly involved in the stability of the complex with DNA [11]. No complete structure has yet been determined for the integrase protomer ($IN^{1–288}$), or for oligomers or complexes of these structures with DNA, due to poor solubility and interdomain flexibility problems.

Integrase functions in a multimeric form, as shown by complementation experiments: mixtures of proteins, each individually inactive, were found to be active. For example, an inactive catalytic triad mutant can be complemented by an inactive integrase truncated at its C-terminal end. Such functional complementation can be observed in virions. In addition, the factors promoting integrase multimerization such as Zn^{2+} also stimulate the specific Mg^{2+}-dependent activity of the enzyme, indicating that the functional enzyme is multimeric. Dimers form at either end of the viral DNA molecule. These dimers are responsible for 3'-processing activity [12]. Pairs of dimers bring together the two ends of the viral DNA and lead to the formation of a tetramer (dimer of dimer), the active form for concerted integration. During its catalytic cycle, IN must bind simultaneously to the viral substrate DNA and the target DNA. Current knowledge of the organization of this tetramer onto DNA is based exclusively on models constructed from partial structural and biochemical (cross-linking and site-directed mutagenesis) data [13]. In a recent model, an IN tetramer is bound to the two ends of the viral DNA, *i.e.* LTRs (Long Terminal Repeat), and to a 26 base pairs host DNA molecule in the presence of Mg^{2+}. This model takes into account the structural constraints deduced from the model of the complex formed between DNA and a related enzyme, the Tn5 transposase, and the observation that the two ends of the viral DNA are integrated five base pairs apart, corresponding to a distance of about 16 Å. This model may provide a platform for the rational design of new inhibitors. It is important to note that most of these models support a symmetrical form of IN for concerted integration [14]. However, recently, Ren *et al.* have proposed an asymmetric tetramer/DNA model for the concerted integration suggesting that at least a reaction intermediate could be asymmetric.

MATERIALS AND METHODS

RCSB- Present study carried out in 2022; July to September at Acharya Nagarjuna University, Guntur, Andhra Pradesh, India. Atomic-level three-dimensional (3D) structure data for biological macromolecules often prove critical to dissecting and understanding the precise mechanisms of action of cancer-related proteins and their diverse roles in oncogenic transformation, proliferation, and metastasis. They are also used extensively to identify

potentially druggable targets and facilitate the discovery and development of both small-molecule and biological drugs that are today benefiting individuals diagnosed with cancer around the world [15]. 3D structures of biomolecules (including proteins, DNA, RNA, and their complexes with one another, drugs, and other small molecules) are freely distributed by the open-access Protein Data Bank (PDB). This global data repository is used by millions of scientists and educators working in the areas of drug discovery, vaccine design, and biomedical and biotechnology research. The US Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) provides an integrated portal to the PDB archive that streamlines access for millions of worldwide PDB data consumers worldwide. Herein, we review online resources made available free of charge by the RCSB PDB to basic and applied researchers, healthcare providers, educators and their students, patients and their families, and the curious public [16]. We exemplify the value of understanding cancer-related proteins in 3D with a case study focused on human papillomavirus.

Swiss model- Homology modeling has matured into an important technique in structural biology, significantly contributing to narrowing the gap between known protein sequences and experimentally determined structures. Fully automated workflows and servers simplify and streamline the homology modeling process, also allowing users without specific computational expertise to generate reliable protein models and have easy access to modeling results, their visualization, and interpretation. Here, we present an update to the SWISSMODEL server, which pioneered the field of automated modeling 25 years ago and has been continuously further, developed. Recently, its functionality has been extended to the modeling of homo- and heteromeric complexes. Starting from the amino acid sequences of the interacting proteins, both the stoichiometry and the overall structure of the complex are inferred by homology modeling. Other major improvements include the implementation of a new modeling engine, ProMod3, and the introduction of a new local model quality estimation method, QMEANDisCo[17].

H-DOCK- Protein-protein and protein-DNA/RNA interactions play a fundamental role in a variety of biological processes. Determining the complex structures of these interactions is valuable, in which molecular docking has played an important role. To automatically make use of the binding information from the PDB in docking, here we have presented HDOCK, a novel web server of our hybrid docking algorithm of template-based modeling and free docking, in which cases with misleading templates can be rescued by the free docking protocol. The server supports protein-protein and protein-DNA/RNA docking and accepts

both sequence and structure inputs for proteins [18]. The docking process is fast and consumes about 10-20 min for a docking run. Tested on the cases with weakly homologous complexes of <30% sequence identity from five docking benchmarks, the HDOCK pipeline tied with template-based modeling on the protein-protein and protein-DNA benchmarks and performed better than template-based modeling on the three protein-RNA benchmarks when the top 10 predictions were considered. The performance of HDOCK became better when more predictions were considered. Combining the results of HDOCK and template-based modeling by ranking first of the template-based model further improved the predictive power of the server. The HDOCK web server is available at http://hdock.phys.hust.edu.cn/ [19].

3D-ligand site- 3DLigandSite is a web server for the prediction of ligand-binding sites. It is based upon successful manual methods used in the eighth round of the Critical Assessment of techniques for protein Structure Prediction (CASP8). 3DLigandSite utilizes protein-structure prediction to provide structural models for proteins that have not been solved. Ligands bound to structures similar to the query are superimposed onto the model and used to predict the binding site. In benchmarking against the CASP8 targets 3DLigandSite obtains Matthew's correlation coefficient (MCC) of 0.64, and coverage and accuracy of 71 and 60%, respectively, similar results to our manual performance in CASP8. In further benchmarking using a large set of protein structures, 3DLigandSite obtains an MCC of 0.68. The web server enables users to submit either a query sequence or structure. Predictions are visually displayed via an interactive Jmol applet. 3DLigandSite is available for use at http://www.sbg.bio.ic.ac.uk/3dligandsite [12].

RESULTS

Swiss Model

Oligo-State Ligands GMQE QMEANDisCo Global

Homo-dimer 2 xARS, 2 xLF2 0.78 0.80 ± 0.05

(Matching prediction)

2 x ARSENIC

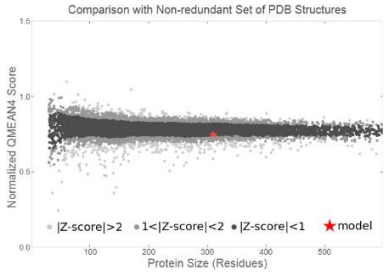
2 x (2S)-[6-bromo-4-(4-chlorophenyl)-2-methylquinolin-3-yl](test-butoxy)ethanoic acid

LF2.3: 13 residues within 4Å:

9 PLIP interactions:

LF2.6: 13 residues within 4Å:

9 PLIP interactions:



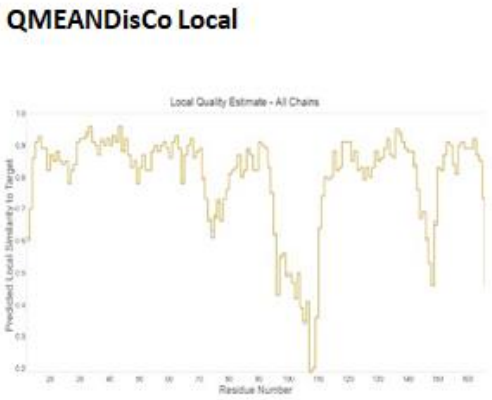


Figure 1; Figure demonstrates the swiss model and interaction residues

Template Seq Identity Coverage Description

4gvm.1.A 99.38% Gag-Pol polyprotein

HIV-1 Integrase Catalytic Core Domain A128T

Mutant Complexed with Allosteric Inhibitor

Model-Template Alignment

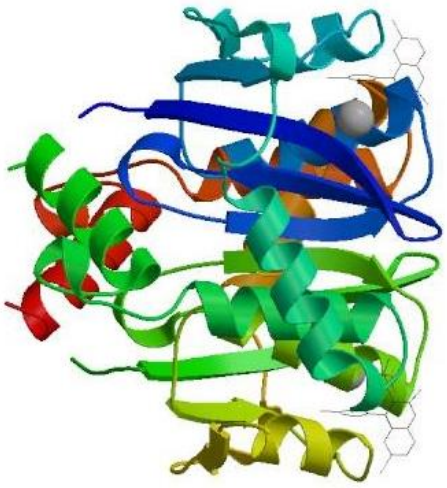


Figure 2; Figure demonstrates the model after template alignment

Global model evaluation- GMQE and QMEANDisCo global give an overall model quality measurement between 0 and 1, with higher numbers indicating higher expected quality. GMQE is coverage dependent, i.e. a model covering only half of the target sequence is unlikely to get a score above 0.5. QMEANDisCo on the other hand evaluates the model 'as is' without explicit coverage dependency (Figure 1).

Global Model Quality Estimate **(**GMQE) is a quality estimate, which combines properties from the target-template alignment and the template structure. They are combined using a multilayer perceptron trained to predict the lDDT score of the resulting model. The GMQE is available before building an actual model and is thus helpful in selecting optimal templates for the modeling problem at hand. Once a model is built, the GMQE ((1) in the figure above) gets updated for this specific case by also taking into account the QMEANDisCo global score of the obtained model to increase the reliability of the quality estimation.

QMEANDisCo global score is the average per-residue QMEANDisCo score (see below) which has been found to correlate well with the lDDTscore (Table 1). The provided error estimate is based on QMEANDisCo global scores estimated for a large set of models and represents the root mean squared difference (i.e. standard deviation) between QMEANDisCo global score and lDDT (the ground truth). As the reliability of the prediction depends on model size, the provided error estimate is calculated based on models of similar size to the input (Figure 2).

QMEAN Z-score analysis is deprecated and the GMQE and QMEANDisCo global scores should be consulted for global model quality estimates instead. It is based on 4 statistical potentials of mean force and their linear combination: the "QMEAN" score. All scores, 5 in total, are compared with what one would expect from experimentally determined structures of similar size using Z-scores (4) in the figure above). In other words: How many standard deviations from the mean is my model score given a score distribution from a large set of experimentally determined structures? Z-scores around 0.0, therefore, reflect a "native-like" structure and, as a rule of thumb, a "QMEAN" Z-score below -4.0 indicates a model with low quality. This is illustrated by the "Comparison" plot (5) in the figure above). The x-axis shows protein length (number of residues) (Table 2). The y-axis is the "QMEAN" score. Every dot represents one experimental protein structure. Black dots are experimental structures with a "QMEAN" score within 1 standard deviation of the mean (|Z-score| between 0 and 1), and experimental structures with a |Z-score| between 1 and 2 are grey. The

experimental structure that is even further from the mean is light grey. The actual model is represented as a red star.

1. Global Model Quality Estimate (GMQE)-0.78; QMEAND is Co Global 0.80±0.05
2. Oligo state: Homodimer 2xARS, 2xLF2
3. 2xArsenic: 4 residues with in 4A: No protein ligand interaction detected.
4. 2x2(S)-[6 bromo-4(4-chloro phenyl) 2-methyl quinolin 3y)] (tert-butoxy)ethanoic acid.
5. 13 residues within 4A: 9PLIP interaction:
6. It is a gap pol polyprotein.
7. HIV-1 integrase catalytic core domain A128T mutant complexes with allosteric inhibitor.

H-Dock:

Table 1; Complex Template Information

Molecule	PDB ID	Chain ID	Align_length	Coverage	Seq_ID (%)
Receptor	6L0C	A	170	1.000	100.0
Ligand	4RXL	A	234	1.000	100.0

Table 2; Summary of the Top 10 Models

Rank	1	2	3	4	5	6	7	8	9	10
Docking Score	-275.34	-233.78	-229.88	-228.67	-222.95	-222.42	-221.57	-221.27	-219.99	-218.60
Ligand rmsd (Å)	91.97	76.31	78.30	68.29	72.37	84.40	81.61	89.79	75.39	85.84
Interface residues	model_1	model_2	model_3	model_4	model_5	model_6	model_7	model_8	model_9	model_10

1. The rank of these models.
2. The docking energy scores.

3. The ligand RMSDS from the input structure or modeled structures by homology modeling.

4. The interface residues within 5.0 A^{o} from their interacting partner or each other, and the corresponding distances.

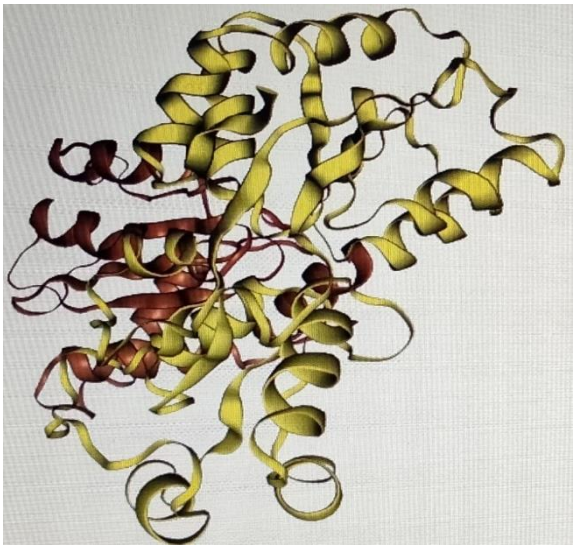


Figure 3; A model of inhibitor and viral protein after docking

Our research interests focus on molecular modeling, bioinformatics, and computational biophysics/biology for protein/RNA structure prediction and interactions, including protein-ligand and interactions, protein-protein interactions, protein-RNA interactions, and modeling of quantitative structure-function relationships (Figure 3 and table 3).).The long-term goal is to develop a set of powerful computational algorithms/software for molecular modeling and engineering, reveal molecular pathways of enzymes by studying the interactions of biological molecules such as proteins and DNA/RNA in cells, and design clinically efficient drugs for diseases by the accurate prediction of bio-molecular interactions (Figure 4).

3.3 D-ligand site:

Table no 3: Ligand Clusters Identified; Note Prediction based on the first cluster

MAMMOTH Scores

Cluster	Ligands	Structure	Av	Min	Max
1	9.8	3	9.4	16.9	17.1
1	9.8	3	9.4		
1	9.5	3	9.4		
1	9.5	3	9.4		
1	9.4	3	9.4		
1	9.4	3	9.4		

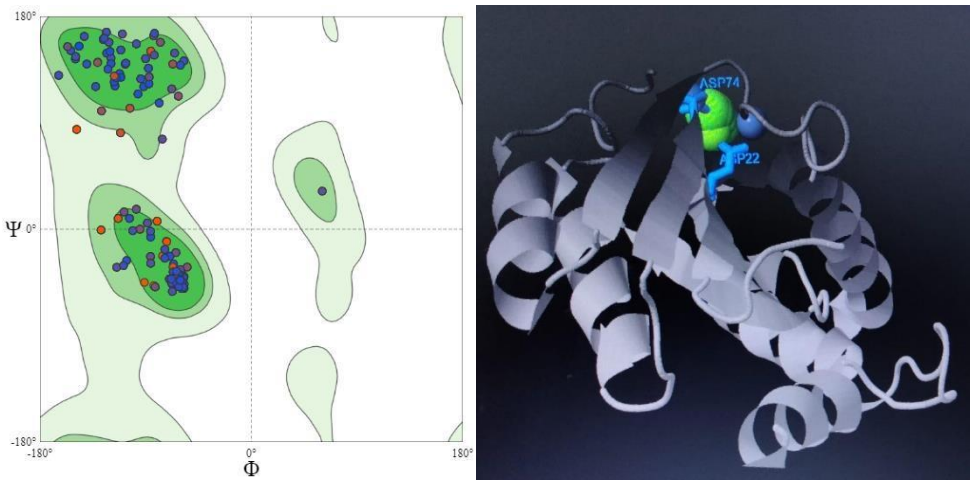


Figure No 4; A ramaplot and validation of the model

DISCUSSION

The left window is a Jmol applet that displays the modeled structure. The residues predicted to form part of the binding site are colored blue [20]. The ligands that form the cluster used for the prediction are also displayed with metal ions shown in space fill format and nonmetal ligands as wireframes. The JAVA runtime environment is required to use the Jmol applet and is freely available from www.java.com if it is not already installed on your system. The right panel provides the user with a range of viewing options to modify the display of the protein, binding site prediction, and ligands in the J-Mol applet [21-22]. The top section controls the display of the whole protein, allowing either a cartoon, space fill, or wireframe

representation. The residues can be colored according to the prediction or by their conservation score (Jensen-Shannon divergence) a key at the bottom of the panel provides a guide for the residue coloring. Further options are available to modify the display of the residues predicted to form the binding site and the ligands used to make the prediction [23-25]. Further, the protein can be colored to show the predicted binding site or the Jensen-Shannon divergence score. Predicted residues can also be labeled for easier identification. Finally, the user can change the background color of the Jmol applet and set the protein to rotate.

The tautomerism and corresponding transition states of diketoacid,, -diketotriazole, dihydroxypyrimidine carboxamide, and 4-quinolone-3-carboxylic acid were calculated using density functional theory (DFT) at the B3LYP/6-311++ G(d,p) level using the Gaussian 03 suite of programs [26]. These substances are each the main component and putative chelating moiety of four well-known INSTIs: some INSTIs can have many tautomers, just like many organic compounds. The keto-enol acid derivates, a fundamentally novel class of INSTIs identified, serve as one prominent example [27]. Because of their tautomerism, they are frequently called "diketo acids." The design of new chelating moieties was aided by the detailed geometric and energetic clarification of these compounds' tautomerism and how the many potential tautomers could chelate.

The Human Immuno Deficiency Virus type 1 HIV-1 integrase is an emerging target for novel anti-viral drugs. Quantitative structure-activity relationship RCSB, SWISS-MODEL, HDOCK, and 3D LIGAND SITE and computational tools models used for HIV-1 integrase inhibitors have developed to understand the protein-ligand interactions to aid in the drug design of more effective analogs [28-30]. HIV (*human immunodeficiency virus*) is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases. It is spread by contact with certain bodily fluids of a person with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV), or through sharing injection drug equipment [31]. This study comprehensively covers the mechanisms of action and inhibitor design for HIV-1 integrase. It serves as a resource for scientists facing challenging drug design issues and researchers in antiviral drug discovery.

CONCLUSION

HIV (*human immunodeficiency virus*) is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases. It is spread by

contact with certain bodily fluids of a person with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV), or through sharing injection drug equipment. The Human Immuno Deficiency Virus type 1 HIV-1 integrase is an emerging target for novel anti-viral drugs. Quantitative structure-activity relationship RCSB, SWISS-MODEL, HDOCK, and 3D LIGAND SITE and computational tools models used for HIV-1 integrase inhibitors have developed to understand the protein-ligand interactions to aid in the drug design of more effective analogs. This study comprehensively covers the mechanisms of action and inhibitor design for HIV-1 integrase. It serves as a resource for scientists facing challenging drug design issues and researchers in antiviral drug discovery. The treatment of HIV 1 infection and AIDS requires interventions of several therapeutic where the affinity of each drug may vary due to multiple target sites. Hence there is a continuous need of therapeutics to combat viral infection and immune compromising syndrome.

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