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Research Article

Investigation of the Molecular Docking of Integrase Strand Transfer Inhibitors Using the Molecular Model of the Catalytic Core of HIV Integrase [PDB ID: 6WC8]

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Abstract

The HIV integrase enzyme, comprising its N-terminal (NTD), central (CD), and C-terminal (CTD) domains, plays a crucial role in the integration of the HIV genome into host DNA and in the viral life cycle. It accomplishes this by recognizing and binding viral DNA, maintaining structural integrity, and catalyzing integration into the host genome. The CTD domain contains the catalytic core, which includes the DDE motif, essential for cleavage and joining reactions, and interacts with LEDGF/p75 to enhance the specificity and efficiency of integration. Inhibitors that block integrase improve HIV treatment and reduce resistance. We utilized molecular docking methods to investigate the catalytic core of HIV integrase and its interactions with inhibitory ligands. The physicochemical properties and pharmacokinetics of the compounds under investigation were calculated using the SwissADME webtool database. Except for compounds with high molecular weight, the remaining compounds exhibit high gastrointestinal absorption, allowing for easy entry into the bloodstream. However, they often have low dermal absorption, which limits their effectiveness for dermal delivery. Compounds with CID numbers 74071, 24800940, and 133081875 demonstrate high dermal absorption. The compound with CID number 91899501 is the only exception, as the other compounds studied bind to a specific site composed of several amino acids. These amino acids, including Gln62, Leu63, Asp64, Val77, His114, Thr115, Asp116, Gly140, Ile141, and Glu152, are crucial for the effective binding of compounds to the enzyme. Understanding the binding sites of integrase strand transfer inhibitors (INSTIs) is crucial for assessing the efficacy of antiretroviral therapy against HIV. The active site of integrase contains the key amino acids D64, D116, and E152, which are targeted by most of the INSTIs studied. Our study aims to enhance the effectiveness of INSTIs and prevent the development of resistant viruses.

Keywords: HIV integrase, Catalytic Core, INSTIs

Introduction

HIV integrase consists of three main domains: the N-terminal domain (NTD), the central domain (CD), and the C-terminal domain (CTD). Each domain has specific functions that contribute to the integration process's efficiency and specificity (Johnson et al., 2013; Kessl et al., 2009). The NTD plays a crucial role in recognizing and binding HIV integrase to viral DNA. It contains a unique HHCC zinc-binding motif that promotes protein multimerization, essential for its function. The NTD also interacts with the 5' and 3' LTRs of the viral genome, positioning the enzyme for integration. Moreover, it interacts with host chromatin components like the nucleosome, potentially influencing integration site targeting within the host genome. Specific amino acid residues, such as Q148, K156, and K159 in the NTD, are vital for binding to viral DNA extremities (Delelis et al., 2008).

The CD acts as a bridge between the NTD and CTD, maintaining the integration complex's structural integrity and aiding in viral DNA movement between the domains. It is involved in conformational changes during integration, allowing the enzyme to transition from DNA binding to catalysis. Additionally, the CD stabilizes the integration complex, preventing premature disassembly of the protein-DNA complex during the reaction (Eilers et al., 2020; Sala et al., 2016; Maertens et al., 2022; Chiu et al., 2004). The CTD is the catalytic core of HIV Integrase, responsible for integrating viral DNA into the host genome. It contains the DDE motif (D64, D116, and E152 in HIV-1) crucial for cleavage and joining reactions. The CTD interacts with viral DNA at the CA dinucleotide of the 3' LTR and the TA dinucleotide of the 5' LTR. Integration proceeds through a two-step mechanism: 3' processing and strand transfer, resulting in the integration of viral DNA into the host

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genome (Delelis et al., 2008; Maertens et al., 2022; Rocchi et al., 2022). The CTD is highly conserved among retroviruses and transposases, indicating its essential role in integration. Structural studies show that the CTD forms an active site pocket accommodating viral DNA ends and facilitating metal ion interaction required for catalysis (Zhang et al., 2022). The integration mechanism involves a nucleophilic attack by conserved aspartate residues on the 3' hydroxyl group of viral DNA, forming a covalent intermediate. Subsequently, the CTD catalyzes DNA helix opening and formation of a 3' hydroxyl group, leading to integration into the host genome (Eilers et al., 2020; Maertens et al., 2022; Rocchi et al., 2022).

Interaction with host proteins like LEDGF/p75 is crucial for integration. LEDGF/p75, a cellular protein interacting with the CTD of HIV Integrase, enhances integration specificity and efficiency by targeting the enzyme to active transcription units in host chromatin. This interaction, mediated by the CTD binding to a conserved PWWP motif in LEDGF/p75, facilitates recruitment of the integration complex to preferred integration sites (Sala et al., 2016; Maertens et al., 2022).

Methods and Materials

Preparation of the HIV Integrase Catalytic Core Model [PDB ID: 6WC8]:

The molecular model of the HIV-1 integrase catalytic core [PDB ID: 6WC8] was obtained from the RCSB PDB database. The 6WC8 structure represents the HIV Integrase catalytic core in complex with an inhibitor 2-(5-(3-fluorophenyl)-2-(2-(thiophen-2-yl)ethynyl)-1-benzofuran-3-yl)ethanoic acid, crystallized using X-ray diffraction. The structure was determined to a resolution of 1.88 Å, with R-values of 0.238 for the work set, 0.278 for the free set, and 0.242 for the observed data. The protein was expressed in Escherichia coli and contains a mutation. The structure was solved by Gorman and Parker in 2020 (Figure 1) (Zhang et al., 2022).

Ligand Model Preparation

During my research, I found 34 INSTI compounds in the PubChem database, which included commercial drugs and chemical precursors for other drugs. These lists are available on PubChem. The manufacturer's proprietary molecule preparation algorithm was used to prepare the ligand and protein (Figure S1) (Kim et al., 2016; Bitencourt-Ferreira et al., 2019).

Predicting Physicochemical Properties and Pharmacokinetics

To predict the physicochemical properties and pharmacokinetics of the studied compounds, we utilized the SwissADME web tool. This user-friendly platform, accessible at http://www.swissadme.ch, offers a range of quick and reliable predictive models such as the BOILED-Egg, iLOGP, and others to assess important drug development parameters (Daina et al., 2014, 2016, 2017; Yousefi, 2024).

Molecular Docking

We utilized Molegro Virtual Docker (MVD), a versatile and reliable software for molecular docking. This powerful tool predicts the binding affinity and orientation of small molecules to target proteins using advanced computational methods. MVD stands out for its flexible docking algorithm, which considers multiple conformations of both ligand and receptor molecules, ensuring accurate results in both rigid and flexible docking scenarios. Some notable features of MVD include grid-based scoring functions, support for multiple docking engines, and comprehensive output analysis tools, aiding in further exploration of docking results (Bitencourt-Ferreira et al., 2019). Within the Docking Wizard section of the Molegro software, we had the option to choose from various scoring algorithms for docking. We opted for the MolDock Scoring Grid algorithm with a grid resolution of 0.3 Angstroms. Additionally, we selected the MolDock SE algorithm for ligand energy optimization and minimization, conducting 10 iterations of approximately 1500 runs each. In defining the grid for the binding site on the protein target, the Docking Wizard section of the Molegro software allowed us to set grid dimensions. We established grid dimensions along the X axis at 15.21, the Y axis at 5.91, and the Z axis at 3.5. We decided to use the entire protein molecule as the binding site, as we found it to be the most effective binding site within the protein target.

Figure 1. The amino acid sequences of the HIV Integrase catalytic core model [PDB ID: 6WC8], comprising sections 57-141, 152-187, and 192-208. These sequences pertain to the HIV-1 integrase enzyme. In our docking study using the integrase molecular model, the software identified 37 cavities in the model. The amino acids that cover these cavities are shown with a green ribbon at the top of the sequence. Additionally, a blue ribbon at the top of the sequence signifies regions with beta-sheet secondary structure, while a red ribbon above the sequences indicates regions with an alpha helix structure.

Results

Molecular Docking Results of Studied Compounds with the HIV Integrase Catalytic Core Model [PDB ID: 6WC8]

The binding affinity of the studied compounds was correlated with their weight, with lighter compounds exhibiting a higher ligand efficiency index (MolDock Score/Heavy Atoms). Compounds with CID Numbers 135397695, 86767865, 54682040, 91899503, and 511335, respectively, had the highest number of hydrogen bonds with the HIV Integrase catalytic core. The binding sites of compounds with CID Numbers 82264, 75646, 75452, 74071, 67326, 46533, 22720, 11950, 1608, 344784, 511335, and 23390002 include the amino acids Gln62, Leu63, Asp64, Val77, His114, Thr115, Asp116, Gly140, Ile141, and Glu152 of the HIV Integrase catalytic core. The binding site of compounds with CID Numbers 66970, 23067, 24800940, 86767865, and 133081875 includes amino acids Leu63, Asp64, Cys65, Leu74, Thr97, Thr115, Asp116, Asn117, Ser119, and Asn120.

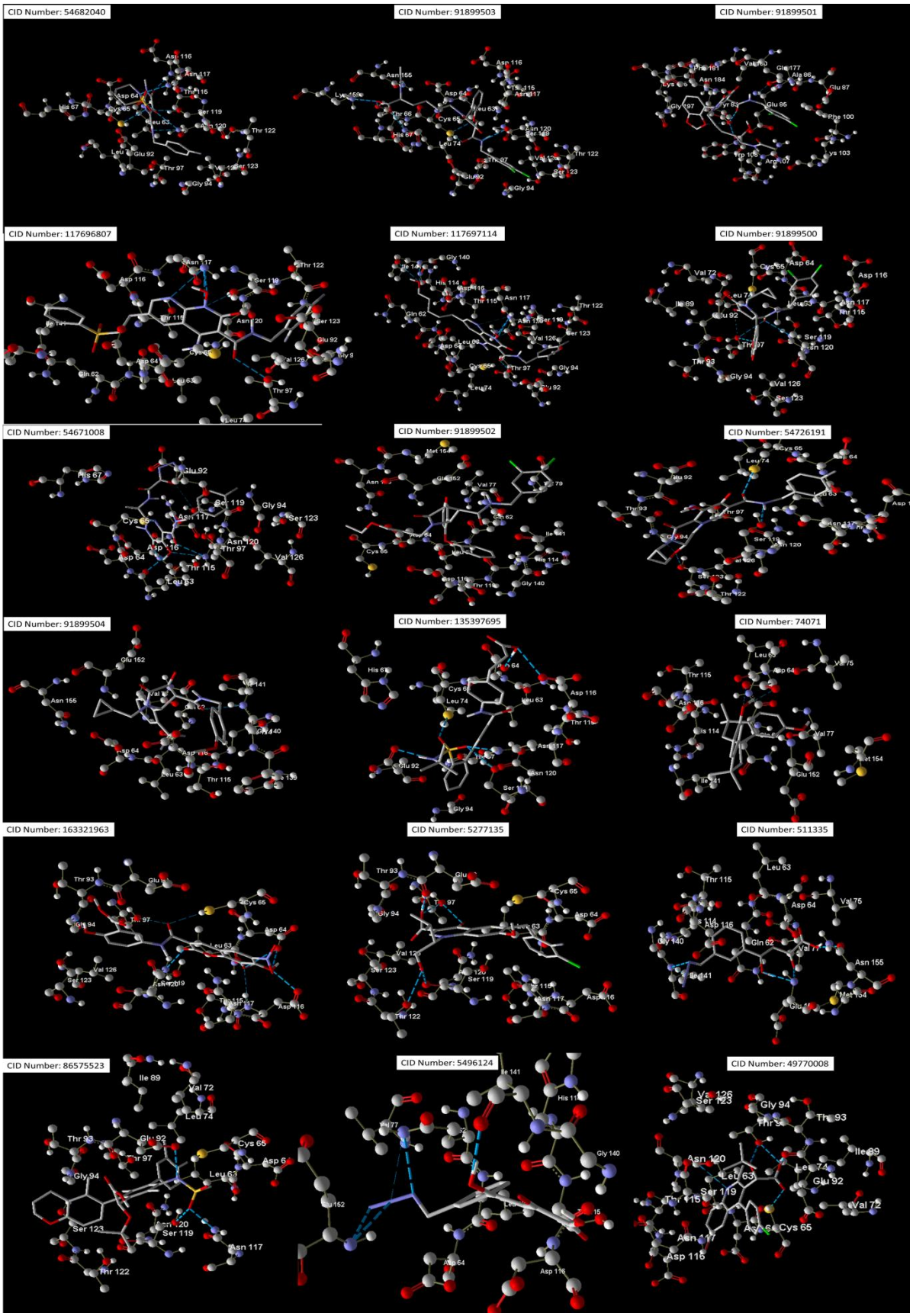
The binding site of compounds with CID Numbers 91899504, 457602, and 5496124 includes the amino acids Gln62, Leu63, Asp64, Val77, His114, Thr115, Asp116, Phe139, Gly140, Ile141, Glu152, and Asn155.

The binding site of compounds with CID Numbers 5277135, 49770008, 54671008, 163321963, 91899500, 86575523, and 54682040 includes amino acids Leu63, Asp64, Cys65, Glu92, Thr93, Gly94, Thr97, Thr115, Asp116, Asn117, Ser119, Asn120, Ser123, and Val126. The binding site of compounds with CID Numbers 135397695, 117697114, 91899502, 91899503, and 117696807 consists of amino acids Gln62, Leu63, Asp64, Cys65, Val77, Val79, His114, Thr115, Asp116, Gly140, Ile141, Glu152, Met154, and Asn155. The binding site of the compound with CID Number 91899501 consists of amino acids Tyr83, Glu85, Ala86, Glu87, Phe100, Lys103, Arg107, Trp108, Gln177, Val180, Phe181, Asn184, Lys185, and Gly197 (Table S1, Figure 1, 2, 3).

Physicochemical Properties of Studied Compounds

The weight of the compounds studied ranges from 71.1 to 592.4 daltons (mean ± SD: 321.58 ±164.29), with several heavy atoms ranging from 5 to 41. The ligand with CID Number 163321963, which has 10 hydrogen bond acceptors and 4 hydrogen bond donors, can create the highest number of hydrogen interactions. The ligand with CID Number 86575523 has the highest molecular refractivity (MR) at 166.46, followed by the ligand with CID Number 91899503 at 152.58.

CID Number 163321963 has the highest total polar surface area of 192.12 Å2. Among the studied compounds, CID Numbers 91899502, 86575523, and 74071 have the highest hydrophobicity based on the iLOGP index. Most of the heavy compounds studied have lower solubility in physiological fluids compared to lighter compounds. Among the medicinal compounds studied, CID Numbers 86575523 and 66970 have the highest solubility in physiological fluids. The compounds with the lowest solubility are CID Numbers 91899502, 86575523, and 49770008 (Table S2 and Figure S1).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CID Number: 91899502
CID Number: 54726191
CID Number: 91899504
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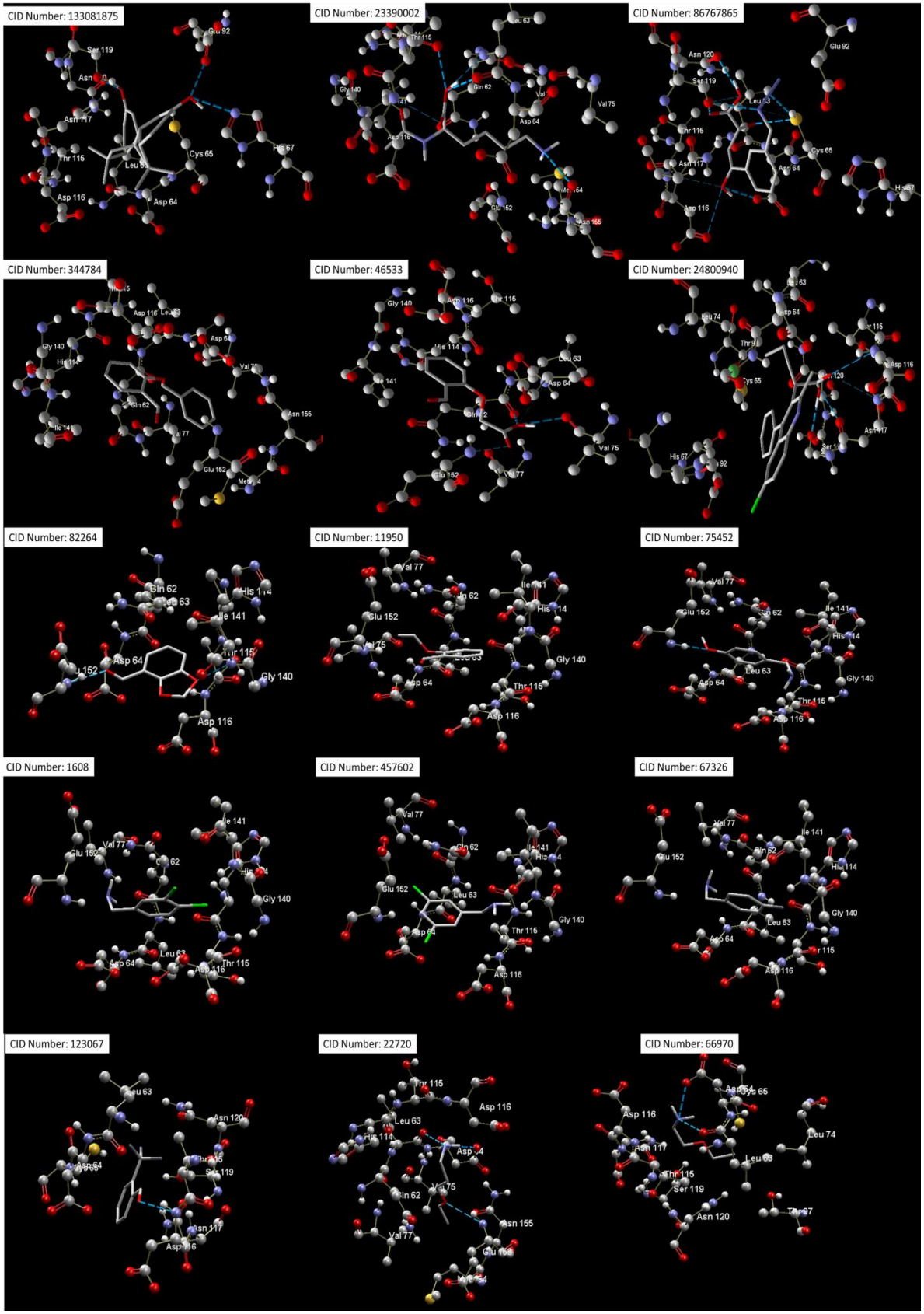
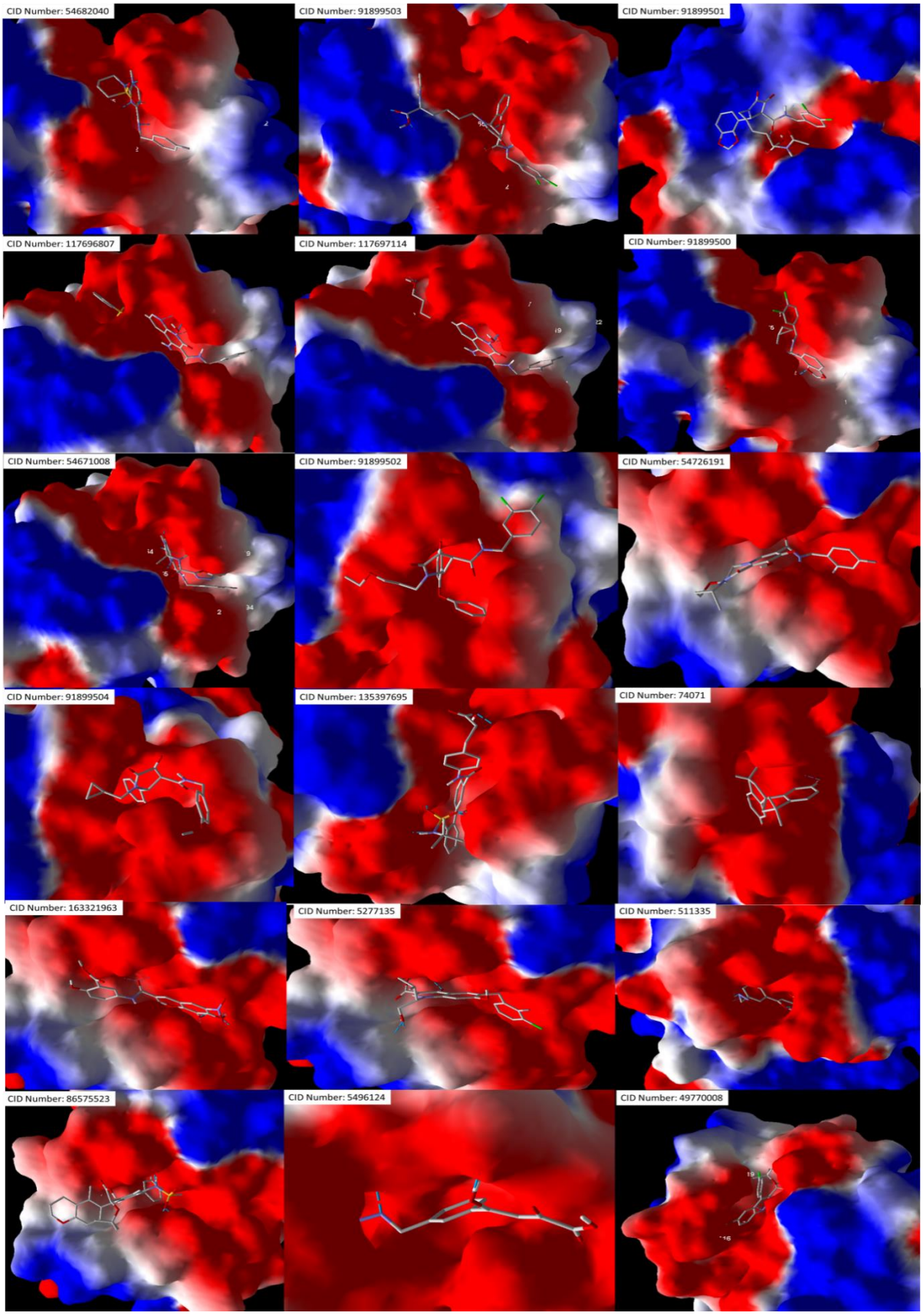


Figure 2. The binding site of the studied HIV-1 integrase inhibitor compounds on the enzyme. Hydrogen bonds are indicated by blue dotted lines. The enzyme model is displayed as a ball and stick model.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CID Number: 54726191
CID Number: 91899504
CID Number: 135397695
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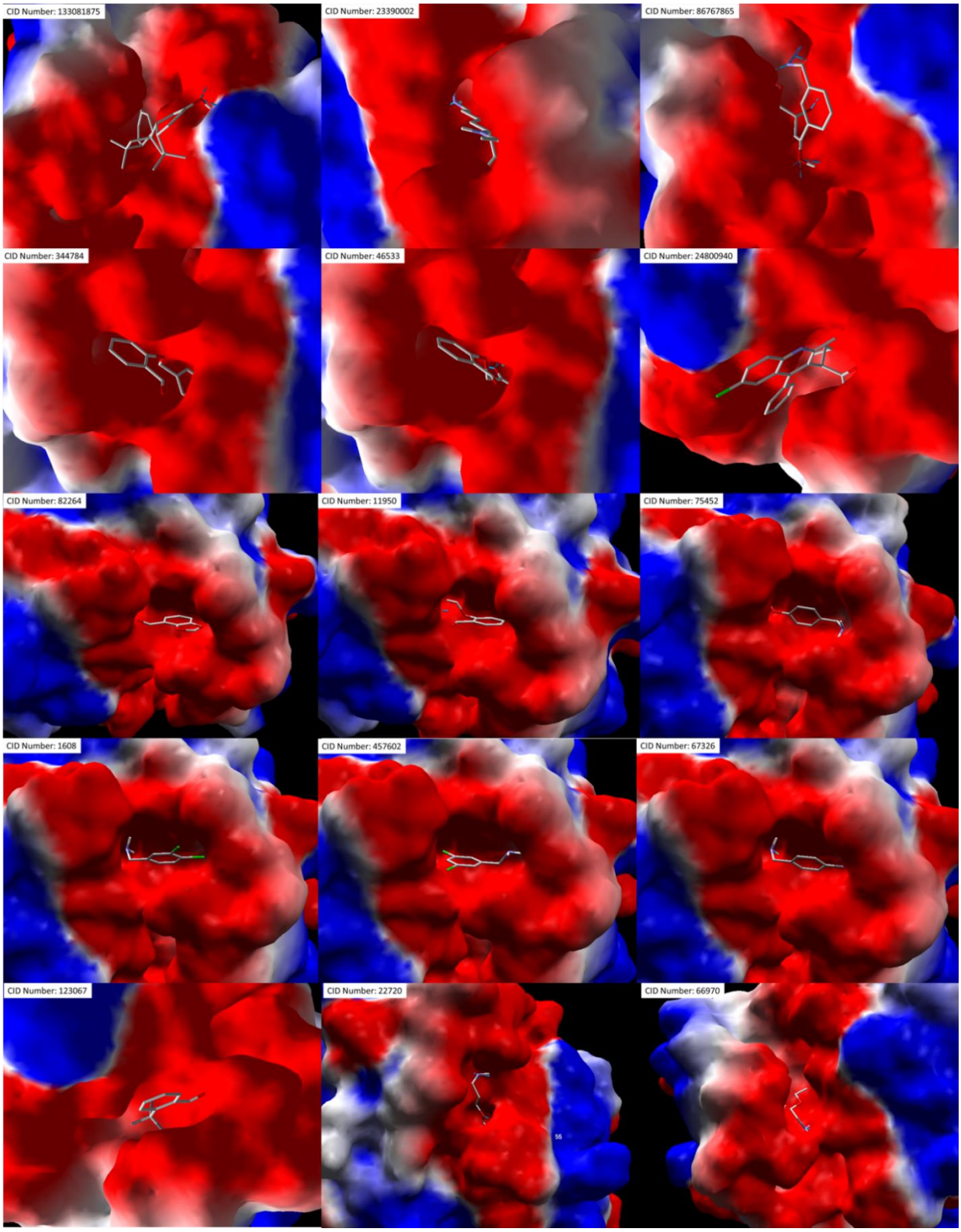

Figure 3. The binding site of the studied HIV-1 integrase inhibitor compounds on the enzyme. The enzyme model is shown as electrostatic surfaces.

Pharmaceutical Properties of Studied Compounds

Most of the compounds studied exhibit high gastrointestinal absorption. Among them, lighter compounds show higher digestive absorption. These compounds are also capable of crossing the blood-brain barrier. Lighter compounds among the medicinal compounds studied do not inhibit

cytochrome P450 enzymes, while heavier compounds often do inhibit these enzymes.

A P-glycoprotein substrate is a substance that utilizes the P-glycoprotein transporter for various activities such as drug absorption and excretion, which can impact the body's pharmacokinetics and alter the effects of other drugs. P-glycoprotein is an efflux pump that plays a crucial role in eliminating xenobiotic and endogenous compounds from the body, significantly affecting the bioavailability and efficacy of various drugs (Daina et al., 2017). In our study, heavier compounds are often P-glycoprotein substrates.

To predict the permeability coefficient (Kp) of compounds through mammalian epidermis, a logarithmic scale is used, with lower values indicating greater permeability. Diclofenac, with a log Kp of -4.96, can cross the skin relatively easily. Most of the studied compounds in our research have poor skin absorption (Daina et al., 2016, 2017). The compounds with the highest rate of skin absorption among the studied drug compounds are those with CID Numbers: 74071, 24800940, 133081875, and 49770008. The Abbot Bioavailability Score (ABS) is a semi-quantitative, rule-based score that predicts the probability of a compound having at least 10% oral bioavailability in rats or measurable Caco-2 permeability. It uses three parameters: total charge, TPSA, and violation of the Lipinski filter, to categorize compounds into four classes with probabilities of 11%, 17%, 56%, or 85%. The primary goal of ABS is to quickly screen chemical libraries and select the most promising molecules for further development in medicinal chemistry projects (Daina et al., 2016, 2017). In our study, the Bioavailability Score for most of the studied compounds was 55%, with the highest Bioavailability Score among the compounds studied being 88%, related to compounds with CID Numbers: 46533, 24800940.

The SwissADME Synthetic Accessibility (SA) Score is a metric that assesses the ease of synthesizing a molecule, with a score ranging from 1 (very easy) to 10 (very hard). The SA score is used to predict the feasibility of synthesizing a compound, with lower scores indicating a higher likelihood of synthesis (Daina et al., 2016, 2017). Most of the compounds studied by us have Synthetic Accessibility scores below 5.0, with lighter compounds often scoring less than 2.0. This indicates that the synthesis of the studied compounds is not difficult (Table 1, Figure S1).

Discussion

Tables 1 and S2 show that most of the studied compounds have high gastrointestinal absorption, indicating that they can be easily absorbed into the bloodstream. However, many of these compounds also have poor skin absorption rates, suggesting that they may not be effective for transdermal delivery. Compounds with CID Numbers 74071, 24800940, and 133081875 have high skin absorption rates, indicating they may be suitable for transdermal delivery. The Bioavailability Score indicates that most of the studied compounds have a score of around 55%, suggesting a moderate likelihood of oral bioavailability. However, some compounds have higher scores. The Synthetic Accessibility Score shows that many of the studied compounds have scores below 5.0, indicating they are relatively easy to synthesize. Tables 1 and S2 provide valuable information about the physicochemical and pharmaceutical properties of the 34 studied compounds.

Understanding the binding sites of Integrase Strand Transfer Inhibitors (INSTIs) and the mutations associated with resistance to these compounds is crucial for understanding the efficacy of antiretroviral therapy for HIV infection. In our study, the binding sites consist of key amino acid residues D64, D116, and E152 that play catalytic roles in the HIV Integrase catalytic core. Specifically, almost all of the studied compounds bind to a sequence consisting of the amino acids Gln62, Leu63, Asp64, Val77, His114, Thr115, Asp116, Gly140, Ile141, and Glu152. These residues are essential for the effective binding of these compounds to the enzyme. Raltegravir was the first INSTI to be approved by the FDA in 2007. It functions by binding to the integrase enzyme and blocking the strand transfer step of HIV-1 DNA integration. With a half-life of approximately 9 hours, RAL requires twice-daily dosing for optimal efficacy. It is active against a broad range of HIV-1 strains, including those that are multidrug-resistant. The emergence of resistance to RAL is associated with mutations at the integrase active site, particularly N155H and Q148K/R/H. These mutations can reduce the susceptibility of the virus to RAL, highlighting the importance of monitoring for resistance development during treatment (Mbhele et al., 2021; Hicks et al., 2009; Delelis et al., 2010).

Elvitegravir is another INSTI that demonstrates efficacy against both HIV-1 and HIV-2. It boasts a more favorable pharmacokinetic profile compared to RAL, allowing for once-daily dosing in combination

with a ritonavir booster to enhance its bioavailability. The most commonly observed resistance mutations with EVG include E92Q, T66I/A/K, T124A, P145S, and Q148K/R. These mutations can arise from the selection pressure imposed by the drug, reducing its antiviral activity. However, EVG is generally well-tolerated and is effective in treatment-naive and treatment-experienced patients (Lampiris., 2012; Rhee, 2019; Trivedi et al., 2020)

Dolutegravir is an INSTI with a high genetic barrier to resistance, meaning that it requires multiple mutations for the virus to become resistant. It has a particularly potent inhibitory activity against HIV-1, with an IC50 value of 2.7 nM. DTG is often used in first-line ART regimens due to its high efficacy and tolerability profile. It is usually administered with other antiretroviral agents to prevent the emergence of resistance. Resistance to DTG has been linked to mutations such as R263K and S230R, as well as changes in the 3'-polypurine tract (3'-PPT) of the viral genome. These mutations can confer varying degrees of resistance to INSTIs (Trivedi et al., 2020; Osterholzer et al., 2014; K Narang et al., 2014; Oliveira et al., 2014).

Bictegravir is a newer INSTI that has a unique inhibition profile compared to RAL and EVG, allowing for once-daily dosing without the need for a pharmacokinetic booster. It has shown efficacy against a wide range of HIV-1 strains and is less likely to induce resistance mutations than other INSTIs. Resistance to BIC is associated with mutations such as M50I/R263K, which occur less frequently than with DTG and EVG. Its favorable resistance profile and convenience of dosing make it an attractive option in the management of HIV infection (Trivedi et al., 2020; Tsiang et al., 2016; Neogi et al., 2018).

BMS-707035 is a structural analogue of RAL with an improved specificity profile. Despite its potential, the development of this compound was halted due to systemic toxicities observed in a 12-month dog safety study. However, research into similar molecules with optimized properties and reduced toxicity continues, as they may offer promising alternatives (Trivedi et al., 2020; Oliveira et al., 2014; Neogi et al., 2018; Korolev et al., 2011; Bar-Magen et al., 2010).

Conclusion

The emergence of resistance to integrase strand transfer inhibitors (INSTIs) underscores the importance of understanding the molecular mechanisms of drug resistance and developing new antiretroviral agents. Each INSTI has a distinct profile that impacts its clinical utility and treatment protocols. Research on the binding sites of INSTIs and resistance mutations is essential for creating effective antiretroviral therapy, enabling clinicians to adjust treatment strategies and enhance patient outcomes by monitoring resistance mutations and modifying regimens as needed.

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Conflict of interests
None.

Supplementary File: Figure S1, Table S1, S2.

Table 1. Pharmaceutical Properties of Studied Compounds.

CID Number	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)	Bioavailability Score	Synthetic Accessibility
91899503	Low	No	Yes	No	No	Yes	Yes	Yes	-7.05	0.55	4.54
91899501	Low	No	Yes	No	No	Yes	No	Yes	-7.41	0.17	4.64
117696807	Low	No	No	Yes	Yes	No	No	No	-7.84	0.55	3.65
117697114	High	No	Yes	No	No	No	No	No	-7.21	0.55	3.32
91899500	High	No	Yes	No	Yes	Yes	Yes	Yes	-6.18	0.55	3.89
54671008	Low	No	Yes	No	No	No	No	Yes	-8.23	0.55	3.49
91899502	High	No	Yes	No	Yes	Yes	Yes	Yes	-5.58	0.55	4.3
54682040	High	No	Yes	No	No	No	No	No	-9.0	0.55	3.83
54726191	High	No	Yes	No	No	No	No	No	-7.13	0.55	4.16
91899504	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-6.25	0.55	3.66
135397695	Low	No	No	No	Yes	Yes	No	Yes	-6.33	0.56	3.39
74071	High	Yes	Yes	Yes	No	Yes	Yes	No	-4.04	0.55	3.31
163321963	Low	No	Yes	Yes	No	Yes	No	No	-6.94	0.55	3.34
5277135	High	No	No	No	Yes	Yes	No	Yes	-5.25	0.56	3.51
511335	High	No	No	No	No	No	No	No	-5.95	0.56	2.69
86575523	Low	No	Yes	No	No	No	Yes	Yes	-5.04	0.56	5.06
5496124	High	No	No	No	No	No	No	No	-5.95	0.56	2.69
49770008	High	No	No	No	Yes	Yes	No	No	-4.88	0.85	3.47
133081875	High	Yes	Yes	No	Yes	Yes	No	Yes	-4.56	0.55	5.93
23390002	High	No	No	No	No	No	No	No	-10.61	0.55	1.95
86767865	High	No	No	No	No	No	No	No	-5.95	0.56	2.69
344784	High	Yes	No	Yes	Yes	No	Yes	No	-5.32	0.55	1.74
46533	High	Yes	No	No	No	No	No	No	-6.82	0.85	1.68
24800940	High	No	No	Yes	Yes	Yes	No	Yes	-4.35	0.85	3.2
82264	High	Yes	No	Yes	No	No	No	No	-6.36	0.55	2
11950	High	Yes	No	Yes	No	No	No	No	-5.73	0.55	1.17
75452	High	Yes	No	Yes	No	No	No	No	-6.54	0.55	1
1608	High	Yes	No	Yes	No	No	No	No	-5.61	0.55	1.17
457602	High	Yes	No	Yes	No	No	No	No	-5.5	0.55	1.15
67326	High	Yes	No	Yes	No	No	No	No	-6.21	0.55	1
123067	High	Yes	No	No	No	No	No	No	-5.39	0.55	1.1
22720	High	No	No	No	No	No	No	No	-7.03	0.55	1.17
66970	High	No	No	No	No	No	No	No	-7.2	0.55	1
75646	High	No	No	No	No	No	No	No	-6.71	0.55	1

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