ISSN: 2357-0547 (Print)
ISSN: 2357-0539 (Online)

Research Article / JAPR / Sec. D
Yousefi, 2024, 8 (3), 176-187

Journal of Advanced Pharmacy Research

Section D: Clinical Pharmacy & Pharmacology

Docking Study of HIV-1 Reverse Transcriptase (HIV-1 RT) with Well-Known Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

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Submitted on: 08-05-2024; Revised on: 11-06-2024; Accepted on: 26-06-2024

To cite this article: Yousefi, R. Docking Study of HIV-1 Reverse Transcriptase (HIV-1 RT) with Well-Known Nucleoside Reverse Transcriptase Inhibitors (NRTIs). *J. Adv. Pharm. Res.* **2024**, *8* (3), 176-187. DOI: 10.21608/aprh.2024.288238.1268

ABSTRACT

Objectives: The nucleic acid-binding cleft in HIV-1 reverse transcriptase (HIV-1 RT) is essential because of its interactions with the polymerase and RNase H active sites. Studying its binding sites for nucleoside reverse transcriptase inhibitors (NRTIs) is crucial for understanding how to effectively select drug compounds, properly administer drugs, and prevent drug resistance. **Materials and Methods:** We conducted docking studies using Molegro Visual Docker, and then we used SwissADME software to analyze the physicochemical properties and pharmacokinetics of the compounds. **Results:** The molecular docking results of the studied compounds with the HIV-1 reverse transcriptase model (6ASW) showed that zalcitabine has the highest ligand efficiency for the enzyme model. The binding sites of the studied compounds were investigated, revealing that all the compounds bind to sequences containing amino acids 34, Val 35, and Val 60, or connect to a binding site containing amino acids Val 90, Gln 91, Leu 92, Gln 161, Ser 162, Thr 165, and Gln 182 in the p66 subunit. Only Zidovudine binds to the sequence of amino acids Asp 110, Tyr 183, Asp 186, Lys 220, Gln 222, Met 230, and Gly 231, which are in the active site of the enzyme. **Conclusions:** We emphasize the crucial role of NRTIs' affinity for the enzyme in inhibiting HIV-1 reverse transcriptase. It is important to monitor and understand resistance mutations of the HIV-1 reverse transcriptase enzyme for effective drug administration strategies.

***Keywords**: HIV-1, Reverse transcriptase, Molecular docking*

INTRODUCTION

Reverse transcriptase inhibitors (RTIs) play a significant role in the treatment of HIV and, in some cases, hepatitis B. These crucial antiretroviral drugs primarily target reverse transcriptase, a key viral DNA polymerase responsible for the replication of HIV and other retroviruses. This class of drugs can be divided into four main forms: Nucleoside analog reverse transcriptase inhibitors (NARTIs or NRTIs), Nucleotide analog reverse transcriptase inhibitors (NtARTIs or NtRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), and Nucleoside reverse transcriptase translocation inhibitors (NRTTIs)[1].

The HIV-1 Reverse Transcriptase (RT)

The reverse transcriptase (RT) of HIV-1 is a crucial enzyme in the virus's life cycle, responsible for

converting the single-stranded RNA genome found in visions into double-stranded DNA. This DNA is then inserted into the host genome by the integrase (IN) enzyme. The RT enzyme is an asymmetric heterodimer composed of two related subunits, p66 and p51, which are derived from the cleavage of the Gag-Pol polyprotein by the viral protease (PR). The p66 subunit has 560 amino acids, and the p51 subunit has 440 amino acids, sharing a common amino terminus [2].

The enzymatic functions of RT, DNA polymerase, and RNase H, are essential for the replication process. The larger p66 subunit contains the active sites for both enzymatic activities, while the smaller p51 subunit plays a structural role. The RT heterodimer consists of two distinct domains in p66: polymerase and RNase H. The polymerase domain comprises four subdomains, namely fingers, palm, thumb, and connection, which are also present in p51. However, the positions of these subdomains differ between p66 and p51, contributing to their distinct roles in the RT enzyme [3, 4].

The nucleic-acid binding cleft in HIV-1 RT

The nucleic-acid binding cleft in HIV-1 RT is primarily formed by the p66 subunit's fingers, palm, thumb, connection, and RNase H subdomains. The connection and thumb subdomains of p51 contribute to the floor of this cleft. The binding cleft accommodates the nucleic acid, interacting with both the polymerase and RNase H active sites, which are approximately 17-18 base pairs apart on the substrate. The αH and αI helices of the p66 thumb help position the nucleic acid by interacting with both the primer and template strands[2].

The nucleic-acid binding cleft in HIV-1 reverse transcriptase (RT) is primarily formed by the p66 subunit's fingers, palm, thumb, connection, and RNase H subdomains. The connection and thumb subdomains of p51 contribute to the floor of this cleft. This binding cleft allows the nucleic acid to interact with both the polymerase and RNase H active sites, which are approximately 17-18 base pairs apart on the substrate. The αH and αI helices of the p66 thumb play a crucial role in positioning the nucleic acid correctly by interacting with both the primer and template strands. The polymerase active site, essential for DNA synthesis, is found in the p66 subunit and consists of three carboxylate residues (D110, D185, and D186) in the palm subdomain. These residues bind two divalent ions, typically magnesium ions in vivo, which are crucial for catalysis. The YXDD motif, highly conserved in retroviral RTs, includes the carboxylate residues D185 and D186. Other conserved residues contribute to the dNTP binding site, such as R72 and K65, which bind the β- and γ-phosphates of the incoming dNTP, and Y115, which helps bind the deoxyribose ring and acts as a steric gate that differentiates between deoxy and ribonucleoside triphosphates. Additionally, Q151 interacts directly with the 3'-OH of the incoming dNTP[2,5].

The highly efficient dNTP binding process in HIV-1 RT, as observed in kinetic studies, is more efficient when using DNA/DNA substrates compared to RNA/DNA substrates. The rate of nucleotide incorporation (kpol) is also found to be higher when using RNA/DNA substrates. Transient kinetics experiments have identified the conformational change in the "fingers" subdomain of RT as the rate-limiting step in single nucleotide incorporation. Steady-state kinetic experiments suggest that the overall reaction is limited by RT's dissociation from the nucleic acid substrate. Nucleoside reverse transcriptase inhibitors (NRTIs), a class of antiretroviral drugs, target HIV-1 RT and function as chain terminators upon incorporation into viral DNA. They can form stable dead-end complexes with RT, potentially hindering viral replication progression. The chemical step of nucleotide incorporation requires two divalent metal ions, primarily magnesium ions, which facilitate the reaction by coordinating the incoming dNTP's phosphates and the three catalytic aspartate residues (D110, D185, and D186) in the polymerase active site. This coordination allows for the 3'-OH group's attack on the alpha-phosphate of the incoming nucleotide and stabilizes reaction intermediates. Structural studies suggest that the YMDD loop in the polymerase active site may contribute to unfavorable interactions with the extended primer terminus, implying that translocation occurs after dNMP incorporation. The pyrophosphate product is likely released before the translocation of RT[2, 5-7].

Nucleoside analog reverse transcriptase inhibitors (NARTIs or NRTIs)

NRTIs and NtRTIs work in a similar way, competing with natural deoxynucleotides for incorporation into the viral DNA chain. By doing so, they effectively cause chain termination, which halts viral DNA synthesis. This mechanism is crucial for preventing the virus from replicating and spreading within the host. However, NRTIs undergo further metabolism in the body, converting into NRTI triphosphates. These metabolites can lead to mitochondrial impairment, resulting in side effects such as lactic acidosis. Some well-known NRTIs include Zidovudine (Retrovir, AZT, or azidothymidine), the first FDA-approved antiretroviral drug used to treat HIV infections and prevent mother-to-child transmission of the virus. Another prominent NRTI is Didanosine (Videx and Videx EC), an adenosine analog also used for treating HIV[8].

Zalcitabine (Hivid) is a discontinued dideoxycytidine drug once used for treating HIV but later withdrawn from the market due to side effects. Stavudine

(Zerit and Zerit XR) is a d4T NRTI used in combination with other antiretroviral drugs for HIV treatment. Lamivudine (Zefix and Epivir) is another NRTI approved for treating both HIV and hepatitis B. This dual-purpose drug effectively inhibits the reverse transcriptase enzyme in both viruses, making it a valuable addition to antiviral therapy. Abacavir (Ziagen) is an analog of guanosine used to treat HIV infections, either alone or in combination with other antiretroviral drugs [8, 9].

Emtricitabine (Emtriva and FTC) is structurally similar to lamivudine and is approved for treating both HIV and hepatitis B. This NRTI is often used in combination with other antiretroviral drugs to enhance its effectiveness in suppressing viral replication. Entecavir (Baraclude) is a guanosine analog specifically designed for the treatment of hepatitis B. It works by inhibiting the reverse transcriptase enzyme, preventing the virus from replicating within the host's liver cells. Truvada is a combination of emtricitabine and tenofovir disoproxil fumarate, used to treat HIV infections and for pre-exposure prophylaxis (PrEP) to prevent HIV transmission in high-risk individuals. Azvudine (RO-0622) is another NRTI[8, 9].

NRTI Resistance in HIV

Resistance to NRTIs in HIV, which stands for Nucleoside Reverse Transcriptase Inhibitors, occurs through two primary mechanisms. The first mechanism involves the reduced incorporation of nucleotide analogs into DNA during the reverse transcription process. This reduction happens due to specific mutations in the N-terminal polymerase domain of the Reverse Transcriptase (RT) enzyme, responsible for converting viral RNA into DNA. These mutations can impact the enzyme's affinity or ability to bind to the drug, ultimately leading to resistance [10, 11].

For example, the M184V mutation is known to confer resistance to two NRTIs: lamivudine (3TC) and emtricitabine (FTC). These drugs are commonly used in combination therapies to treat HIV infection. As more mutations accumulate in the RT enzyme, the virus becomes less susceptible to the effects of NRTIs, potentially compromising the effectiveness of antiretroviral therapy [11-13].

The second resistance mechanism involves the excision or hydrolytic removal of the incorporated drug. This process essentially reverses the polymerization reaction, allowing the DNA chain to be extended by releasing the triphosphate drug. This resistance development is driven by excision enhancement mutations, such as M41L, D67N, K70R, L210W, T215Y/F, and K219E/Q. These mutations are particularly selected by thymidine analogs like Zidovudine (AZT) and Stavudine (D4T), which are also NRTIs. Additionally, other mutations, including insertions and deletions, can contribute to NRTI resistance by enhancing the excision process. These resistance mechanisms can make HIV less susceptible to NRTIs, requiring the continuous development of new drugs and treatment strategies to effectively combat the virus. As the virus evolves and develops resistance to existing medications, healthcare professionals must stay informed about emerging therapies and adapt treatment plans accordingly to ensure the best possible outcomes for patients living with HIV [10-13].

MATERIAL AND METHODS

Reverse Transcriptase Model Preparation

The model of HIV-1 reverse transcriptase (RT) (6ASW) was obtained from the Protein Data Bank database at https://www.rcsb.org/structure/6asw.it. It depicts the structure of HIV-1 RT in a ternary complex with double-stranded DNA and an incoming d4TTP (2',3'-didehydro-2',3'-dideoxythymidine-5'-triphosphate) at pH 9.0. They aimed to understand the interaction between HIV-sensitive RT and d4TTP, one of the first chain-terminating nucleoside analogs used to treat HIV infection. The 6ASW structure was obtained using X-ray diffraction at a resolution of 2.60 Å, with R-values for free, work, and observed being 0.220, 0.179, and 0.180, respectively. The HIV-1 RT complex was expressed in Escherichia coli, and the structure contains mutations. For model preparation, we used Molegro Visual Docker software version 5.0 [14, 15].

Ligand Model Preparation:

The molecular models of the ligands Zidovudine, Stavudine, Zalcitabine, Emtricitabine, Abacavir, Entecavir, and Didanosine were obtained from the PubChem database at https://pubchem.ncbi.nlm.nih.gov/compound/. For model preparation, we utilized Molegro Visual Docker software version 5.0 [14, 16].

Predicting Physicochemical Properties and Pharmacokinetics

The SwissADME web tool is an essential resource for researchers involved in drug development. It provides a convenient platform to forecast key parameters such as physicochemical properties and pharmacokinetics. This valuable tool can be accessed without registration at http://www.swissadme.ch, making it easily accessible to a wide range of users. With an intuitive interface and reliable predictive models like BOILED-Egg and iLOGP, SwissADME ensures a seamless experience for users, enhancing their work in drug development [17-21].

Molecular Docking

Molegro Virtual Docker (MVD) is a versatile

and reliable software for molecular docking. It utilizes advanced computational methods to predict the binding affinity and orientation of small molecules to target proteins. MVD's flexible docking algorithm considers multiple conformations of both ligand and receptor molecules, providing accurate results in rigid and flexible docking scenarios. Key features include grid-based scoring functions, support for multiple docking engines, and output analysis tools for exploring docking results. With 32 docking protocols and the ability to consider the presence or absence of water molecules, MVD offers a robust platform for molecular docking analysis [16].

RESULTS

We present the ligand efficiency values (LE1) of studied compounds in their interaction with HIV-1 reverse transcriptase (RT). The highest ligand efficiency for zalcitabine (CID Number 24066) was observed to be -10.081 kcal/mol, while the lowest LE1 for abacavir (CID Number 441300) was -7.460 kcal/mol. Abacavir has the highest interaction energy of -182.209 kcal/mol and the lowest interaction energy is observed for Emtricitabine with -134.314 kcal/mol.

All the studied compounds interact with amino acids from both the p51 and p66 subunits of HIV-1 RT. The p51 subunit involves amino acids Trp 88, Glu 89, Gly 93, Ile 94, Lys 154, Pro 157, Ala 158, Tyr 181, Gln 182, Tyr 183, and Met 184, while the p66 subunit involves amino acids Val 90, Gln 91, Leu 92, Gln 161, Ser 162, Thr 165, and Gln 182.

Additionally, the compounds bind to sites containing specific amino acids from both the p66 and p51 subunits. In the p66 subunit, these amino acids include Gln 23, Trp 24, Pro 25, Leu 26, Lys 30, Ile 31, Leu 34, Val 35, and Val 60, and with Ile 132, Pro 133, Ser 134 in the p51 subunit.

Notably, Zidovudine (CID Number 35370) has a distinct binding site that also involves amino acids from both subunits. In the p66 subunit, these amino acids are Lys 66, Asp 110, Tyr 183, Asp 186, Lys 220, Gln 222, Met 230, Gly 231. In the p51 subunit, they include Lys 65, Lys 66, Val 108, Asp 186, Tyr 188, Met 230, Gly 231, Thr 232, Gln 373, Thr 377, Ala 408, Trp 410.

Physicochemical and Pharmaceutical Properties of Studied Compounds

The molecular weight of the compounds studied ranges from 211 to 286 daltons, with 15 to 20 heavy atoms. Among these compounds, zalcitabine has the highest solubility in physiological fluids. They exhibit low hydrophobicity, with abacavir having the highest level at iLOGP=2.12. These compounds are highly absorbed in the gastrointestinal tract, do not penetrate the blood-brain barrier, and do not inhibit cytochrome P450 enzymes. Their skin penetration is minimal, except for abacavir, which is actively transported into cells by Pgp. The other compounds are not substrates for Pgp (refer to **Table 3** and **Table 4**).

DISCUSSION

The compounds studied, including Zidovudine, Stavudine, Zalcitabine, Emtricitabine, Abacavir, Entecavir, and Didanosine, have molecular weights ranging from 211 to 286 daltons and exhibit low hydrophobicity. They are highly absorbed in the gastrointestinal tract, do not penetrate the blood-brain barrier, and do not inhibit cytochrome P450 enzymes. Abacavir is an exception, as it is actively transported into cells by Pgp. The compounds show varying degrees of skin penetration, solubility, and interactions with specific enzymes and transporters (refer to Table 3 and Table 4). We calculated the ligand efficiency values of various compounds that interact with the HIV-1 reverse transcriptase (RT) enzyme. Zalcitabine has the highest ligand efficiency at 10.081 kcal/mol, while Abacavir has the lowest LE at -7.4606 kcal/mol. The compounds interact with amino acids from both the p51 and p66 subunits of HIV-1 RT, and their binding sites involve specific amino acids from both subunits. The nucleic-acid binding cleft in HIV-1 RT is primarily formed by the p66 subunit's fingers, palm, thumb, connection, and RNase H subdomains, with the p51 subunit's connection and thumb subdomains contributing to the floor of this cleft.

The polymerase active site, essential for DNA synthesis, is found in the p66 subunit and consists of three carboxylate residues that bind two divalent ions, typically magnesium ions in vivo, which are crucial for catalysis. The highly efficient dNTP binding process in HIV-1 RT is more efficient when using DNA/DNA substrates compared to RNA/DNA substrates. The chemical step of nucleotide incorporation requires two divalent metal ions, primarily magnesium ions, which facilitate the reaction by coordinating the incoming dNTP's phosphates and the three catalytic aspartate residues in the polymerase active site. Nucleoside analog reverse-transcriptase inhibitors (NRTIs) function by competing with natural deoxynucleotides for incorporation into the viral DNA chain, effectively causing chain termination and halting viral DNA synthesis. These inhibitors undergo further metabolism in the body, converting into NRTI triphosphates, which can lead to mitochondrial impairment and side effects such as lactic acidosis. NRTIs were the first class of antiretroviral drugs developed to combat HIV and, in some instances, hepatitis B. They operate by mimicking natural nucleosides, which are the building blocks of DNA [22, 23].

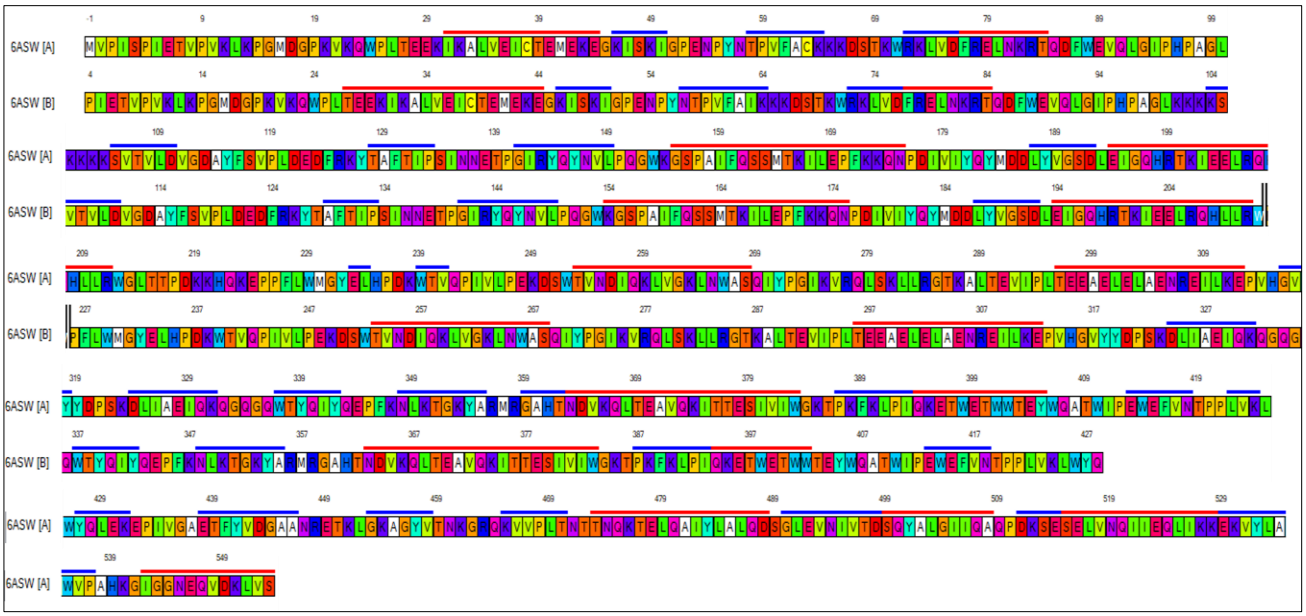


Figure 1. The sequence and secondary structure of the p51 (6ASW[A]) and p66 (6ASW[B]) subunits of the reverse transcriptase enzyme in molecular model [PDB: 6ASW]. Each amino acid is represented by a different letter and color. The secondary structure is depicted as continuous lines above the amino acid sequence, with red indicating alpha helix and blue indicating beta sheet.

Mutation of the residue remaining from the NRTI fusion occurs when it enters the DNA strand. As the virus replicates, mutations can occur in the reverse transcriptase active site or nearby regions. These mutations can alter the enzyme's structure, affecting the drug's ability to bind to the active site and reducing its effectiveness. Different NRTIs may result in distinct mutations. Enhanced phosphorolytic removal, also known as "primer unblocking," is a resistance mechanism that involves mutations increasing the removal of incorporated NRTIs from the viral DNA. This mechanism helps overcome chain termination. Thymidine analog mutations (TAMs) such as M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E are selected by thymidine analogs like zidovudine (ZDV) and stavudine (d4T), contributing to resistance against all NRTIs except lamivudine (3TC). The degree of cross-resistance depends on the NRTI and the number of TAMs present [22-24].

NRTI-associated resistance mutations can lead to multi-resistance, such as the Q151M mutation, which confers intermediate resistance to ZDV, ddI, d4T, and ABC. When combined with other mutations, Q151M can result in high-level resistance to these NRTIs and decreased susceptibility to tenofovir (TDF). Insertions at position 69, in combination with TAMs, can also cause high-level resistance to ZDV, d4T, ddI, ABC, and TDF. When NRTIs are used as monotherapy, resistance patterns can change significantly. For example, using 3TC or FTC with thymidine analogs like ZDV or d4T can delay the emergence of TAMs, preserving future treatment options. However, combining thymidine analogues with ddI increases the risk of cross-resistance. In the case of ABC/3TC, if virological failure occurs, the resistance profile may still preserve future options, as the impact on susceptibility is moderate for ABC and TDF when L74V is present alone or in combination with M184V. The lowest rate of mutation selection was observed when ABC/3TC was used with a boosted protease inhibitor regimen [22, 25].

Combining TDF with 3TC or FTC results in reduced susceptibility to TDF and most other NRTIs when the M184V/K65R profile is present. However, the impact of K65R on d4T susceptibility is not fully understood, and more data is needed to determine the resistance profile when TDF/FTC is combined with other antiretroviral agents. Understanding these mutational patterns and their interactions is crucial for effective HIV-1 treatment strategies and optimizing the selection of antiretroviral agents. Regular monitoring of treatment response and early intervention in case of virological failure can help preserve treatment options and prevent the development of drug-resistant viral strains. Triple-NRTI therapies like ABC/3TC/ZDV have shown a low rate of resistance mutations at failure, potentially safeguarding future treatment options. However, ABC/3TC/TDF has exhibited high rates of virological failure, with patients developing both M184V and K65R mutations. Other NRTI combinations, such as 3TC/ddI/TDF and CBV/TDF, have also demonstrated high rates of failure [26].

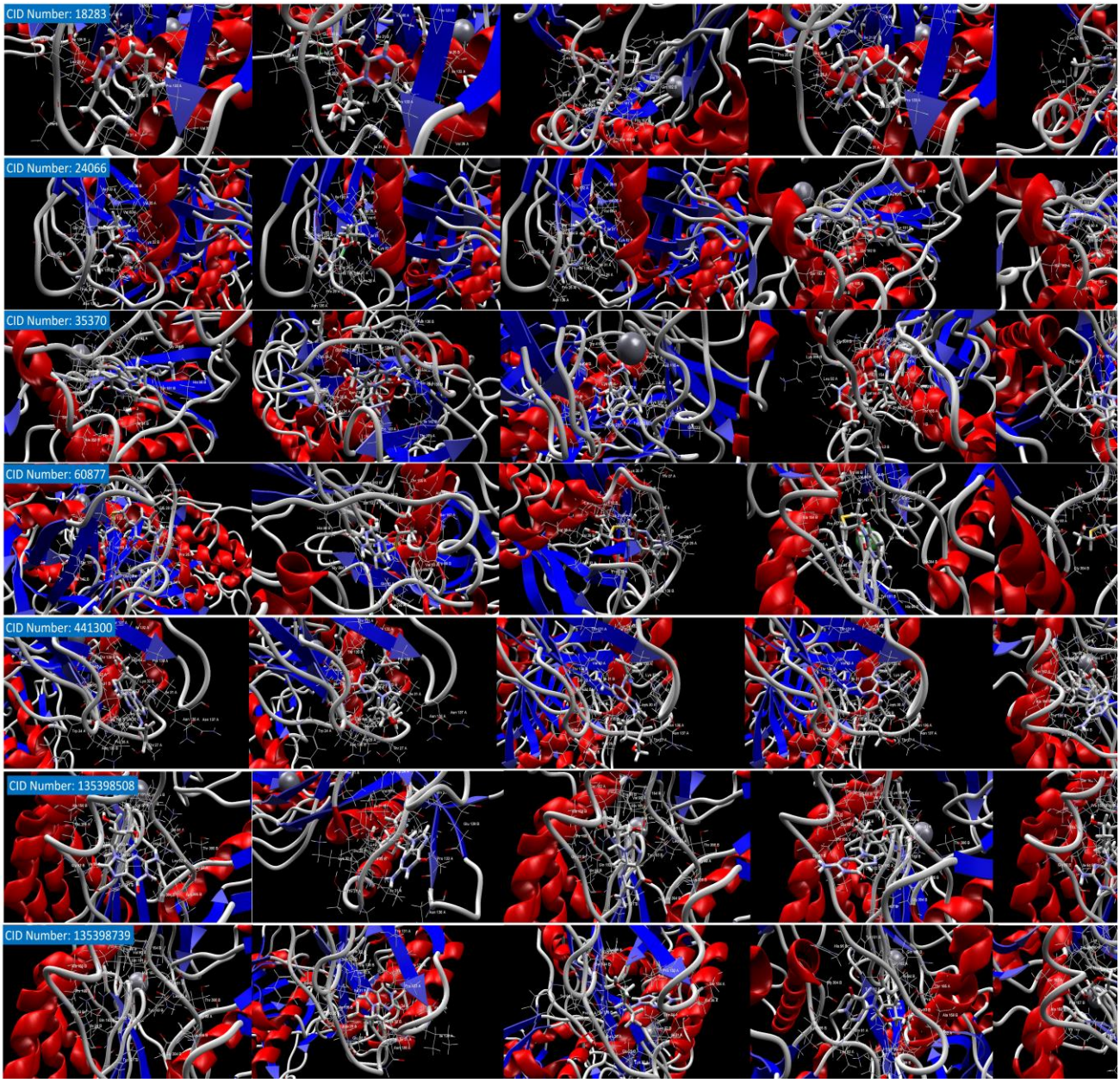


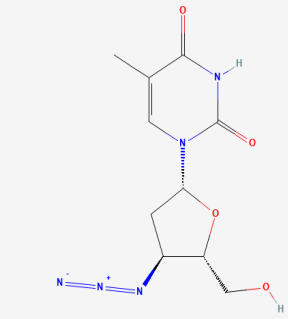
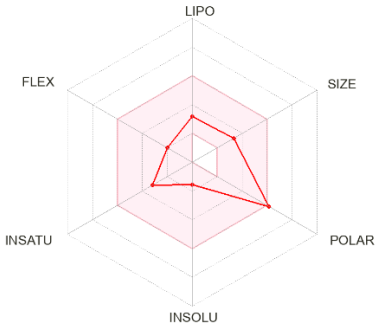
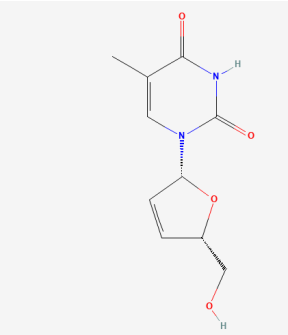
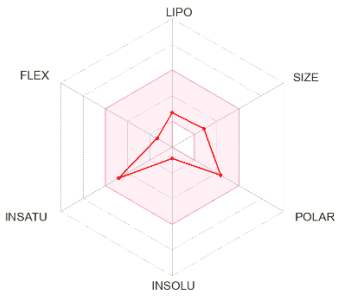
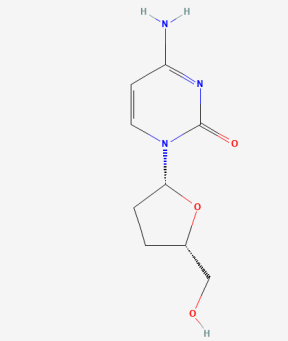
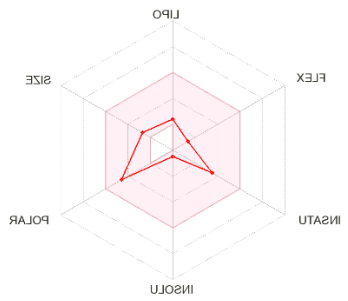
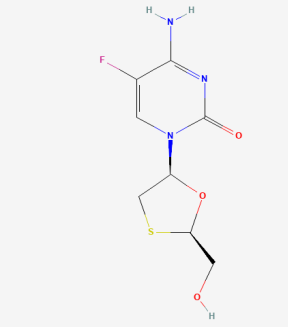
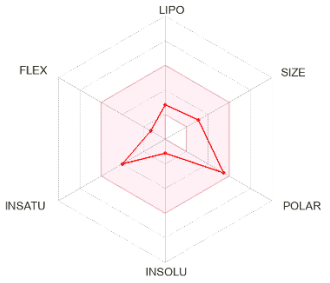
Figure 2. The five binding sites with the highest binding affinity of the studied compounds for the reverse transcriptase enzyme model [PDB: 6ASW].

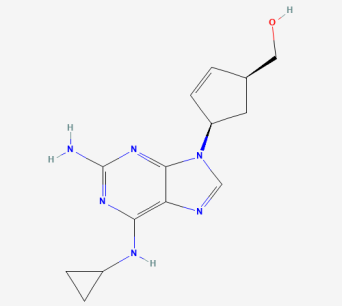
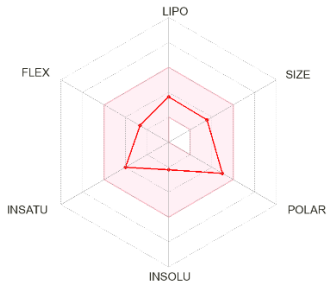
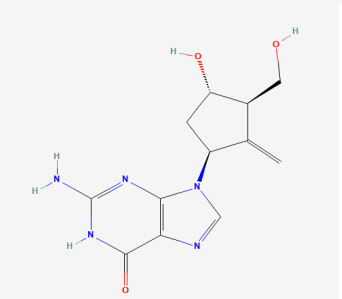
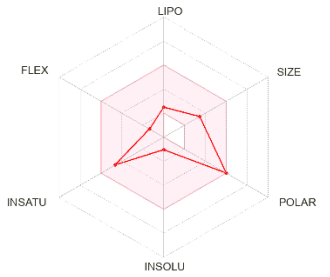
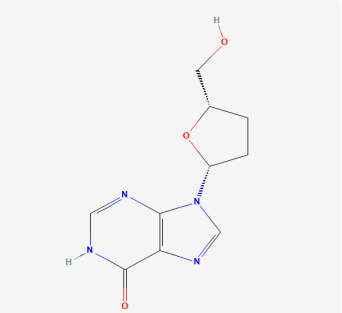
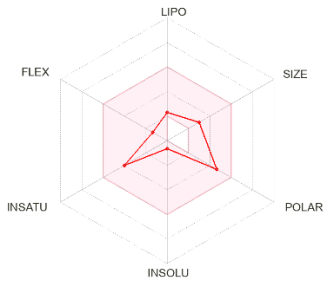
The combination of ZDV given twice daily with TDF once daily as an NRTI backbone may have an antagonistic mechanism of resistance, preventing the emergence of the K65R mutation. This combination should be further explored. To prevent the development of drug-resistant viral strains and maintain treatment options, it is crucial to promptly intervene in cases of treatment failure and monitor the response to antiretroviral therapy. Further research is needed to understand the mutational pathways associated with different NRTI-containing regimens and their implications for future treatment strategies. In clinical practice, it is recommended to use 3TC or FTC in combination with thymidine analogues to avoid ongoing viral replication on NRTI-based regimens. The 215Y TAM pathway should be considered, as it confers higher-level resistance to NRTIs, including ZDV. Maintaining 3TC in a failing regimen is advisable, as it retains partial activity despite the presence of resistance mutations [22-27].

Table 1. The molecular docking results of the studied compounds with the reverse transcriptase enzyme model [PDB: 6ASW].

Binding site (Code)	Ligand	MW	Heavy Atoms	Torsions	Interaction	MolDock Score	HBond	LE1	Docking Score
[00]441300	441300	287.34	21	4	-182.209	-184.755	-3.83604	-8.79787	-186.179
[00]135398739	135398739	236.227	17	2	-180.315	-177.397	-6.77439	-10.4351	-178.249
[02]441300	441300	287.34	21	4	-175.649	-167.686	-2.76394	-7.98505	-165.367
[01]441300	441300	287.34	21	4	-174.338	-172.403	-6.77601	-8.20966	-169.744
[01]35370	35370	271.273	19	4	-173.837	-158.412	-8.21978	-8.33749	-164.153
[03]35370	35370	271.273	19	4	-168.788	-157.844	-11.9171	-8.30759	-163.681
[00]18283	18283	227.237	16	2	-167.5	-156.083	-9.5876	-9.75522	-161.928
[04]135398508	135398508	278.287	20	2	-165.511	-155.491	-9.30623	-7.77454	-157.006
[03]441300	441300	287.34	21	4	-163.545	-158.654	-4.56696	-7.55493	-162.643
[03]18283	18283	227.237	16	2	-162.609	-157.183	-3.18587	-9.82391	-151.849
[02]135398508	135398508	278.287	20	2	-162.579	-151.58	-7.37846	-7.57898	-160.712
[00]35370	35370	271.273	19	4	-162.401	-162.855	-11.4916	-8.57133	-167.727
[01]135398508	135398508	278.287	20	2	-161.209	-158.527	-4.00874	-7.92633	-162.05
[04]441300	441300	287.34	21	4	-159.955	-156.673	-6.84912	-7.4606	-158.496
[00]135398508	135398508	278.287	20	2	-159.142	-157.343	-2.72118	-7.86717	-168.935
[04]35370	35370	271.273	19	4	-159.023	-146.101	-7.58675	-7.68951	-161.289
[01]135398739	135398739	236.227	17	2	-158.962	-156.05	-7.05964	-9.17941	-158.99
[02]24066	24066	212.226	15	2	-158.793	-150.917	-4.74765	-10.0611	-155.171
[00]24066	24066	212.226	15	2	-157.774	-151.227	-11.0152	-10.0818	-159.49
[01]24066	24066	212.226	15	2	-155.756	-149.038	-12.7962	-9.93588	-157.611
[02]35370	35370	271.273	19	4	-155.73	-156.131	-5.08214	-8.21743	-163.749
[03]135398508	135398508	278.287	20	2	-155.583	-153.91	-7.07121	-7.69551	-159.124
[00]60877	60877	248.255	16	2	-154.032	-146.614	-5.99726	-9.16336	-154.441
[03]135398739	135398739	236.227	17	2	-152.71	-150.326	-3.94415	-8.84269	-152.322
[02]135398739	135398739	236.227	17	2	-150.775	-147.908	-4.50585	-8.7005	-152.819
[01]18283	18283	227.237	16	2	-150.304	-149.177	-8.90388	-9.32358	-154.995
[02]60877	60877	248.255	16	2	-147.63	-137.833	-5.9093	-8.61458	-141.015
[04]18283	18283	227.237	16	2	-147.608	-134.935	-6.49756	-8.43342	-138.409
[02]18283	18283	227.237	16	2	-147.3	-145.235	-5.80508	-9.07718	-152.068
[04]135398739	135398739	236.227	17	2	-145.643	-141.571	-3.67838	-8.32771	-145.269
[04]24066	24066	212.226	15	2	-140.95	-125.907	-4.30299	-8.39378	-137.569
[04]60877	60877	248.255	16	2	-140.162	-129.531	-9.1103	-8.09569	-137.842
[03]24066	24066	212.226	15	2	-138.263	-133.286	-6.81436	-8.8857	-144.063
[01]60877	60877	248.255	16	2	-137.916	-133.345	-6.22812	-8.33406	-142.615
[03]60877	60877	248.255	16	2	-134.314	-131.537	-3.47069	-8.22109	-140.517

Table 2. Introduction of Studied Compounds

Drug name	CID number	IUPAC Name	2D-stracture of Studied Compounds	Radar scale of physicochemical properties
Zidovudine	35370	-1[(2R,4S,5S)-4-azido-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione		
Stavudine	18283	1-[(2R,5S)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]-5-methylpyrimidine-2,4-dione		
Zalcitabine	24066	4-amino-1-[(2R,5S)-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one		
Emtricitabine	60877	4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2-one		

Abacavir	441300	[(1S,4R)-4-[2-amino-6-(cyclopropylamino)purin-9-yl]cyclopent-2-en-1-yl]methanol		
Entecavir	135398508	2-amino-9-[(1S,3R,4S)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-1H-purin-6-one		
Didanosine	135398739	9-[(2R,5S)-5-(hydroxymethyl)oxolan-2-yl]-1H-purin-6-one		

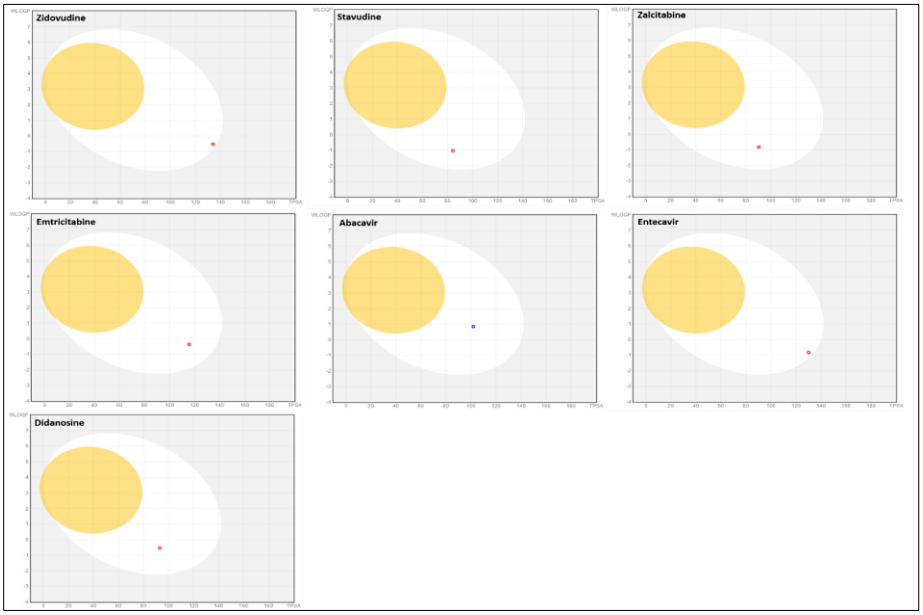


Figure 3. Egg-plot of the studied compounds. The yellow areas represent compounds that passively cross the blood-brain barrier, white areas indicate passive absorption in the digestive system, blue dots show entry through P-glycoproteins, and red dots signify compounds that are removed via glycoproteins in the central nervous system.

Table 3. The physicochemical properties of the studied compounds

Ligands	Zidovudine	Stavudine	Zalcitabine	Emtricitabine	Abacavir	Entecavir	Didanosine
Formula	C10H13N5O4	C10H12N2O4	C9H13N3O3	C8H10FN3O3S	C14H18N6O	C12H15N5O3	C10H12N4O3
MW	267.24	224.21	211.22	247.25	286.33	277.28	236.23
Heavy atoms	19	16	15	16	21	20	17
Aromatic heavy atoms	6	6	6	6	9	9	9
Fraction Csp3	0.6	0.4	0.56	0.5	0.5	0.42	0.5
Rotatable bonds	3	2	2	2	4	2	2
H-bond acceptors	7	4	4	5	4	5	5
H-bond donors	2	2	2	2	3	4	2
MR	61.73	56.44	53.52	56.27	80.4	72.39	58.77
TPSA	134.07	84.32	90.37	115.67	101.88	130.05	93.03
iLOGP	1.76	1.67	1.05	1.2	2.12	0.79	0.88
XLOGP3	0.05	-0.81	-1.3	-0.62	0.87	-1.12	-1.47
ESOL Solubility (mg/ml)	7.29	30.60	67.60	18.40	1.74	24.50	54.30
ESOL Solubility (mol/l)	0.03	0.14	0.32	0.07	0.01	0.09	0.23
ESOL Class	Very soluble	Very soluble	Very soluble	Very soluble	Soluble	Very soluble	Very soluble

Table 4. The pharmaceutical properties of the studied compounds

Ligands	Zidovudine	Stavudine	Zalcitabine	Emtricitabine	Abacavir	Entecavir	Didanosine
GI absorption	High	High	High	High	High	High	High
BBB permeant	No	No	No	No	No	No	No
Pgp substrate	No	No	No	No	Yes	No	No
CYP1A2 inhibitor	No	No	No	No	Yes	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No
log Kp (cm/s)	-7.89	-8.24	-8.51	-8.25	-7.43	-8.79	-8.78

The relationship between TAMs, the K65R mutation, and ZDV susceptibility should also be taken into consideration. Only ZDV remains effective in the presence of the K65R mutation. For patients who have experience with NRTIs and have viruses containing TAMs, the likelihood of K65R selection is minimal when using TDF, as long as TAMs, especially T215Y, are already present (28-30).

By comprehending these resistance patterns and interactions, clinicians can enhance the selection of antiretroviral agents and create successful strategies for treating HIV-1.

CONCLUSION

We emphasize the essential role of NRTIs in treating HIV, stressing the importance of monitoring resistance mechanisms to effectively combat drug-resistant viruses. We discuss complex resistance pathways, including mutations like TAMs in the reverse transcriptase enzyme, advocating for using this understanding to optimize antiretroviral drug selection and treatment approaches for HIV-1 patients. Ultimately, this improves clinical outcomes against evolving viral resistance.

Funding Acknowledgments

None.

Conflict of interest

The author declares that there isn't any conflict of interest regarding the publication of this paper.

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