DRUG LIGAND-BINDING ANALYSIS ON TENOFOVIR AND ZIDOVUDINE AS A REVERSE TRANSCRIPTASE INHIBITOR OF HIV

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Introduction

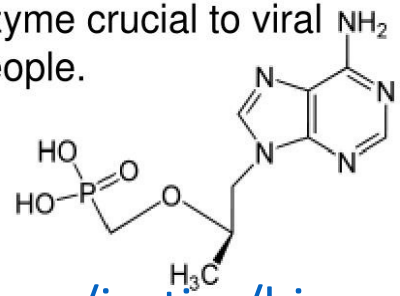
Drug ligand-binding analysis on tenofovir and zidovudine as a reverse transcriptase inhibitor of HIV.

Understanding the mechanism of action of these drugs is crucial for effective HIV treatment.

Ligand-binding analysis provides insights into drug-target interactions and helps in drug development.

Tenofovir

- **Tenofovir disoproxil fumarate** (**TDF** or **PMPA**), marketed by Gilead Sciences under the trade name **Viread**, belongs to a class of antiretroviral drugs known as nucleotide analogue reverse transcriptase inhibitors (NRTIs), which block reverse transcriptase, an enzyme crucial to viral production in HIV-infected people.



Emau P, Jiang Y, Agy MB, *et al.* (2006).

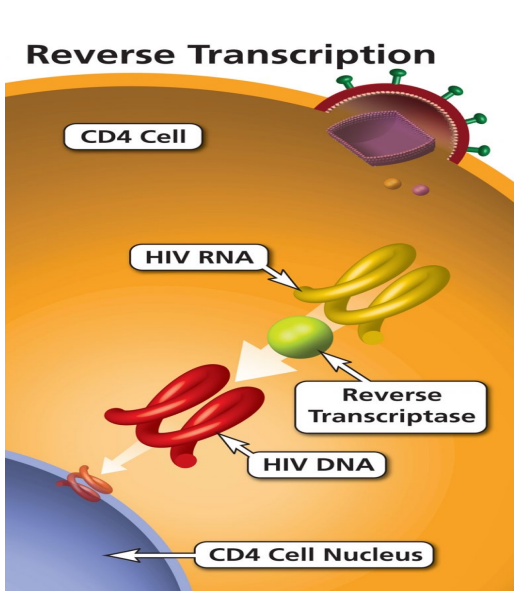
https://www.slideserve.com/justise/hiv

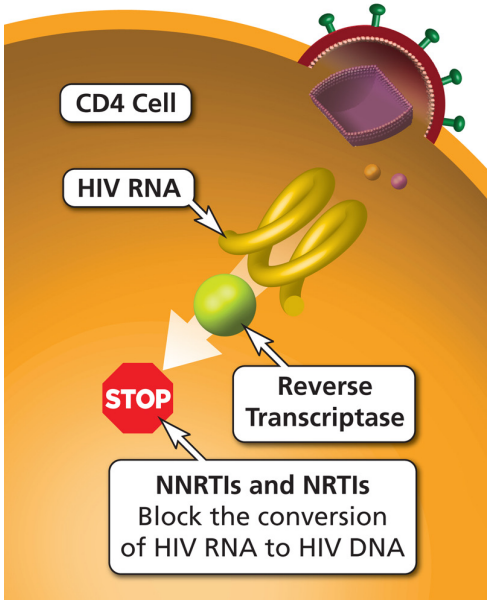
HIV Reverse Transcriptase

HIV reverse transcriptase is an enzyme responsible for converting viral RNA into DNA.

Inhibition of reverse transcriptase is a key strategy in HIV treatment.

Tenofovir and zidovudine are both reverse transcriptase inhibitors.





https://clinicalinfo.hiv.gov/en/glossary/nucleoside-reverse-transcriptase-inhibitor-nrti

Tenofovir

Tenofovir is a nucleotide reverse transcriptase inhibitor (NRTI).

It is converted into its active form, tenofovir diphosphate, in cells.

Tenofovir diphosphate competes with natural nucleotides, leading to chain termination during viral DNA synthesis.

Tenofovir

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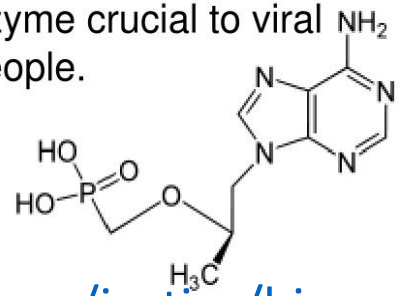

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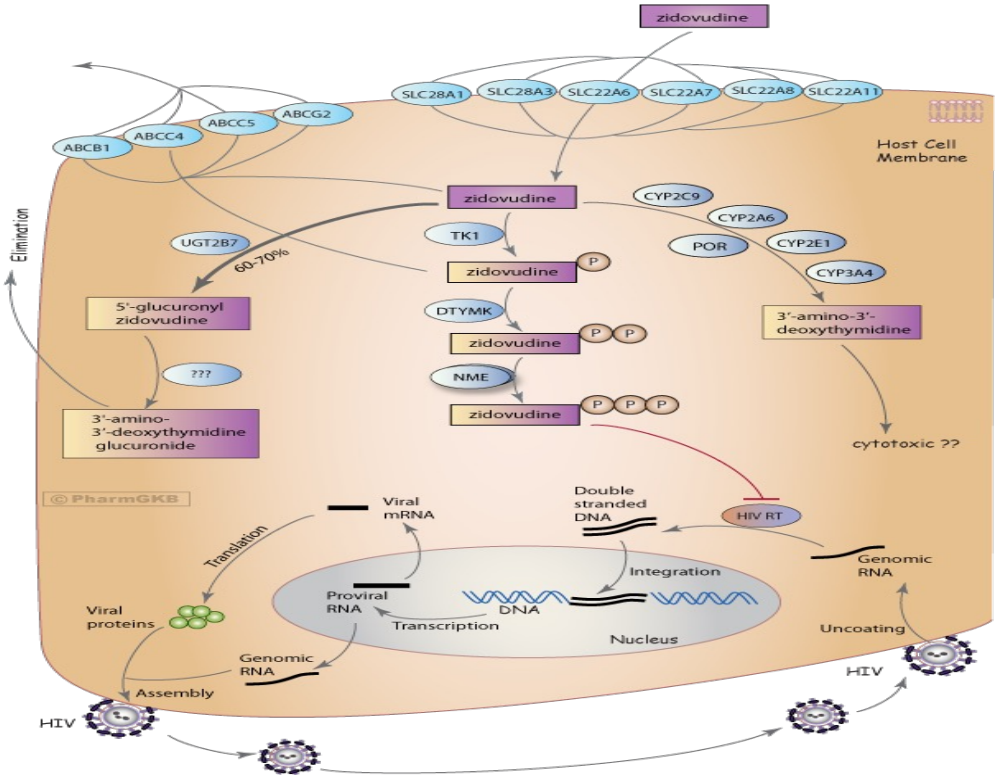
Zidovudine

Zidovudine is also an NRTI and a thymidine analogue.

It undergoes phosphorylation to its active form, zidovudine triphosphate.

Zidovudine triphosphate inhibits reverse transcriptase by acting as a chain terminator.



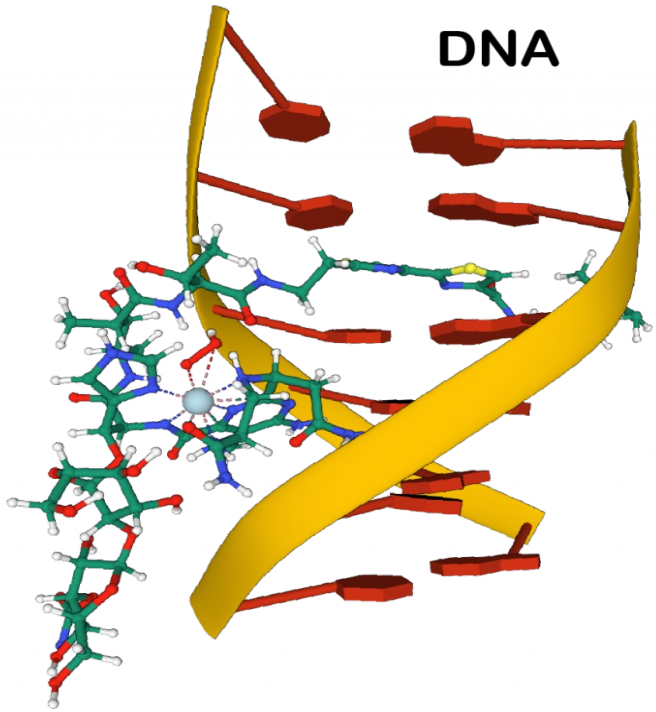
https://www.pharmgkb.org/pathway/PA165859361

Ligand-Binding Analysis

Ligand-binding analysis studies the interaction between a drug (ligand) and its target molecule.

It provides information about binding affinity, kinetics, and structural details.

Various techniques like molecular docking, crystallography, and NMR spectroscopy are used for ligand-binding analysis.



Drug: Bleomycin a2

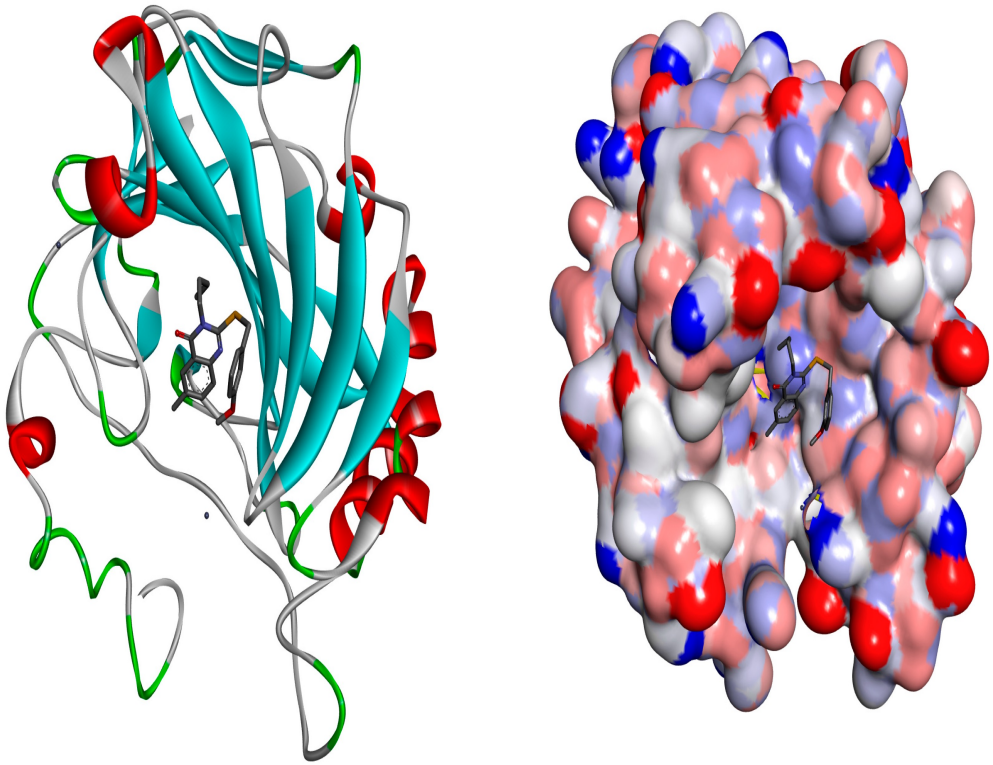
https://www.ebi.ac.uk/training/online/courses/biomacromolecular-structures/ligand-small-molecule-2/

Molecular Docking

Molecular docking predicts the binding pose and affinity of a drug to its target.

It involves the generation of multiple conformations and orientations of the ligand within the target's binding site.

Scoring functions evaluate the binding free energy to rank the ligand poses.

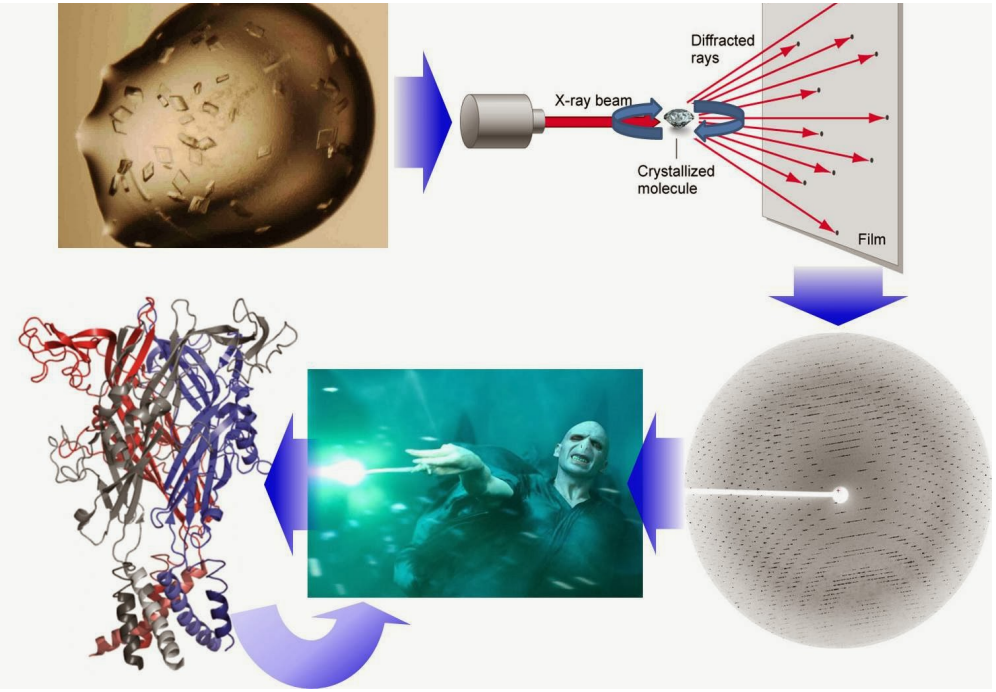


https://ganeshwaghule.blogspot.com/p/molecular-docking.html

Research Objective

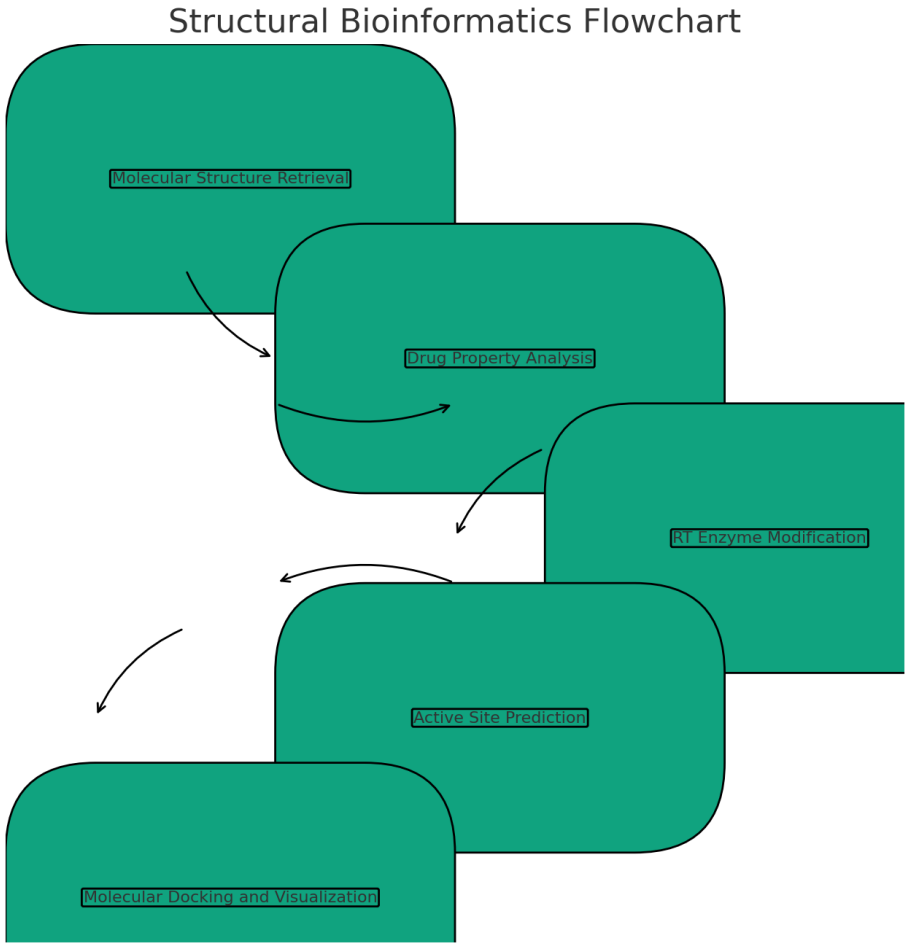
- in silico analyses will be done to examine the pharmacological properties of tenofovir and zidovudine, as well as their binding affinity with HIV-1 RT enzyme.

- Furthermore, the absorption, distribution, metabolism, excretion, and toxicity of both drugs were also examined



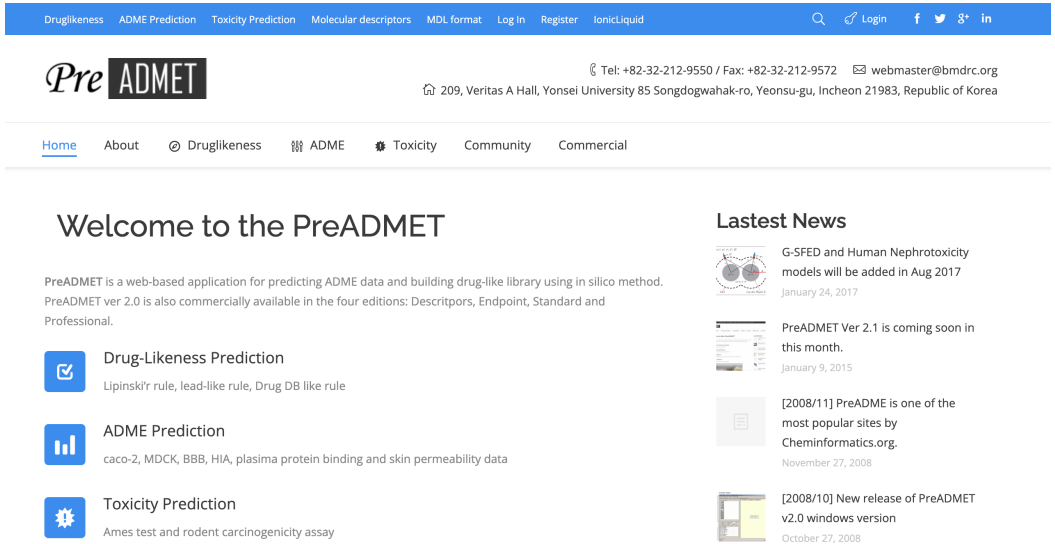
Methodology

- **Molecular Structure Retrieval**: The first step where you obtain the 3D structure of the molecule, usually from databases like the Protein Data Bank (PDB).
- **Drug Property Analysis**: This step involves analyzing the physicochemical properties of the drug molecule, such as hydrophobicity and charge distribution. (preADMET 2.0)
- **RT Enzyme Modification**: This phase focuses on altering the structure of the reverse transcriptase enzyme, possibly to enhance its functionality or specificity. (Pymol 2.5.2)
- **Active Site Prediction**: Here, the active sites on the enzyme where the drug molecule can potentially bind are identified. (CASTp)
- **Molecular Docking and Visualization**: The final step involves simulating the interaction between the drug and the enzyme to predict binding affinity and visualizing the binding pose. (Pyrx)



ADME-TOX analysis of tenovir and zidovudine

- ADMET analysis showed that tenofovir have better Pgp-inhibitor absorption and BBB distribution than zidovudine
- zidovudine possessed higher Fu with carcinogenic properties.
- Both drugs were found to be poor at Caco-2 absorption with high passive MDCK permeability, tested positive for HIA, have up to 30% bioavailability, proper PPB and VD, may act as both CYP substrate and inhibitor, have moderate clearance, long half-life, and exhibited different toxicity and allergic properties.



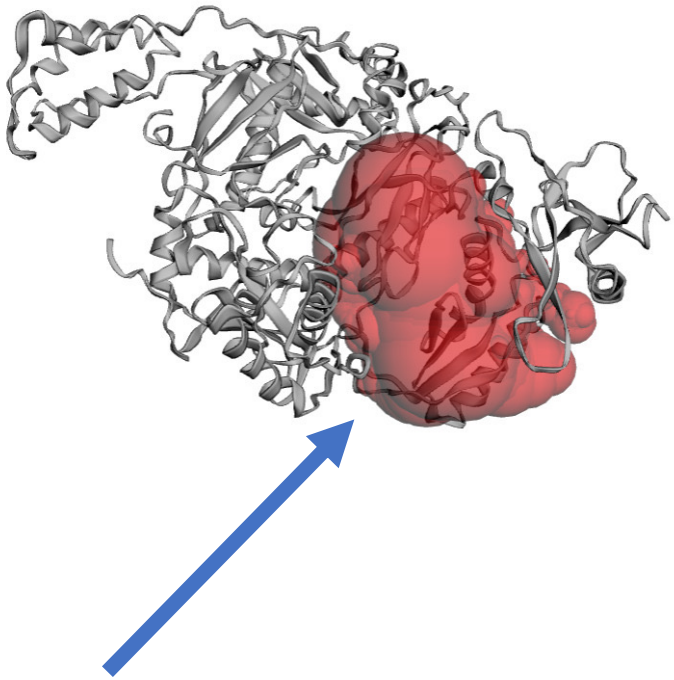
https://preadmet.webservice.bmdrc.org/

Active Site Prediction of RT Enzyme

The deployed structure is the PDB code: 2ZD1

The active site prediction was then done using CASTp, which showed the predicted active site pockets that were then used to confirm whether the molecular docking drug binding results are located on the predicted active sites

It represents the active site (Pocket 1) marked with the color red where the drug binds to the enzyme

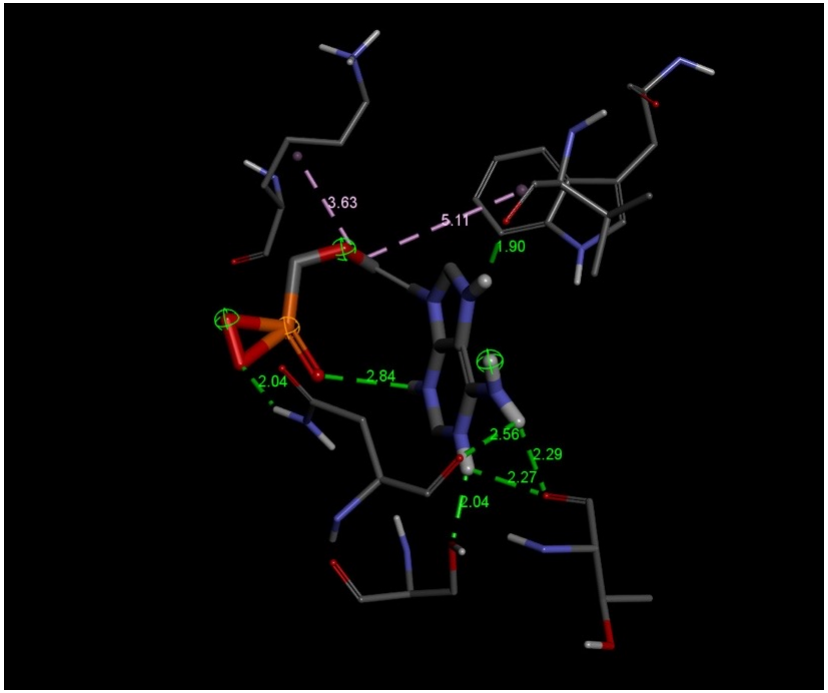


3D Ligand-Binding Analysis of Tenofovir

Molecular docking studies have shown the interaction of tenofovir with the active site of reverse transcriptase.

Crystallographic studies have confirmed the binding mode and interactions of tenofovir with key residues.

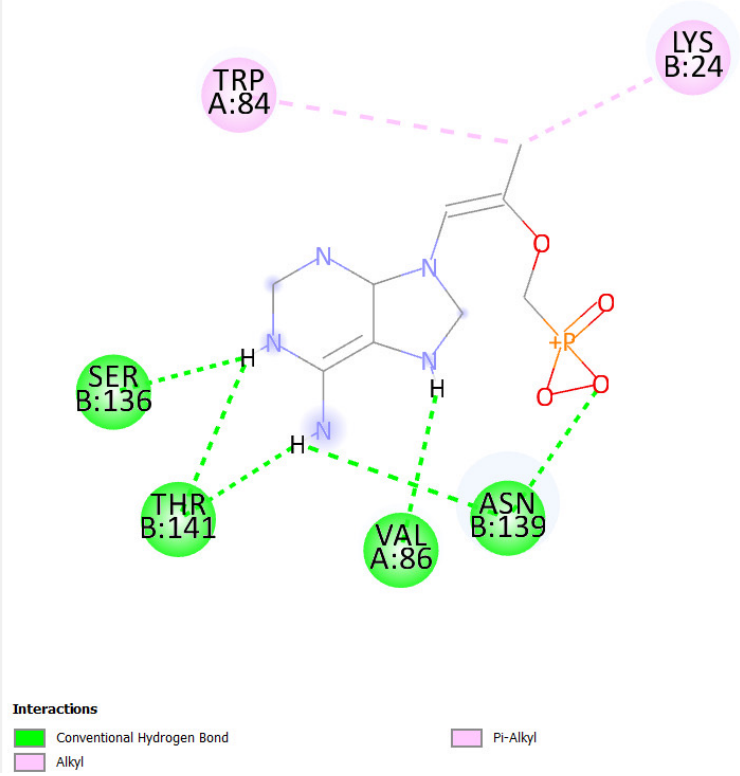
NMR spectroscopy has provided insights into the dynamic behavior of tenofovir in complex with reverse transcriptase.



2D Ligand-Binding Analysis of Tenofovir

Tryptophan 84 and Lysine 24 were found to form alkyl interaction with the drug, with a longer distance of 3.63 and 5.11 Å

Total 2 pi-alkyl bonds, and 6 hydrogen bonds.

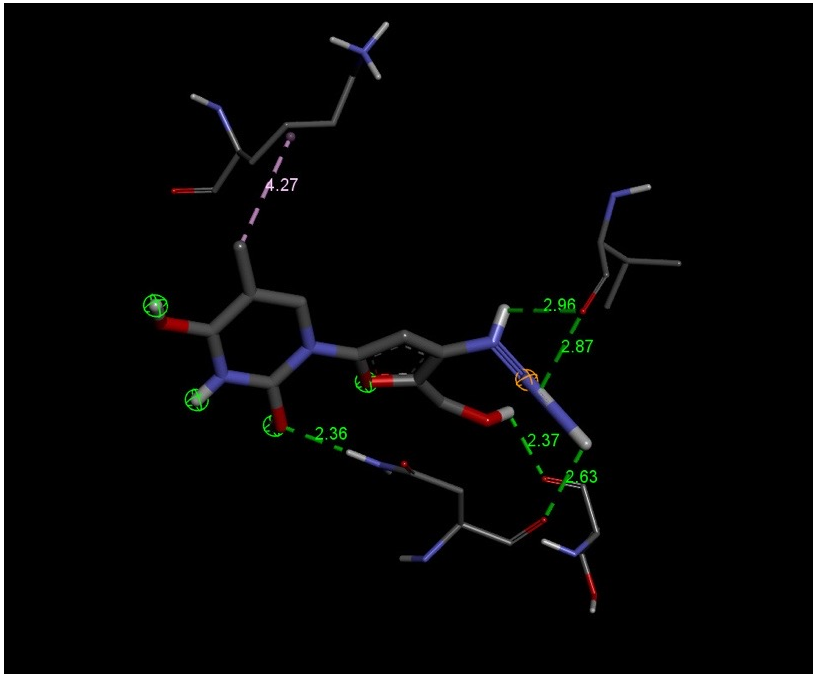


3D Ligand-Binding Analysis of Zidovudine

Molecular docking studies have revealed the binding mode and interactions of zidovudine with reverse transcriptase.

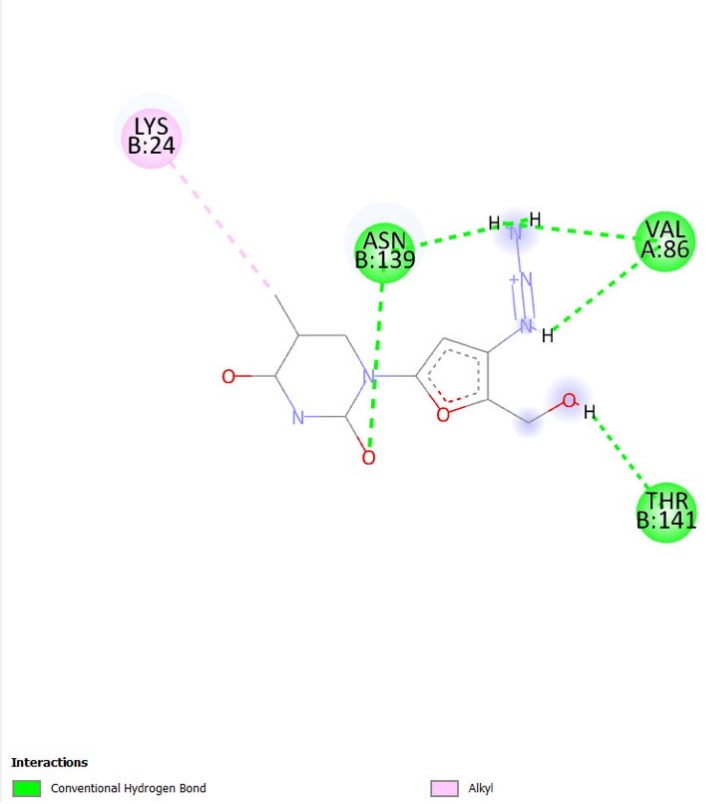
Crystallographic studies have confirmed the positioning of zidovudine within the active site of reverse transcriptase.

NMR spectroscopy has provided insights into the conformational changes induced by zidovudine binding.



2D Ligand-Binding Analysis of Zidovudine

- Similar with tenofovir, the enzyme also shared conventional hydrogen bond and alkyl interactions with zidovudine.
- Valine 86, Asparagine 139, and Threonine 141 formed a conventional hydrogen bond interaction with varying distance from 2.36 to 2.96 Å, whereas only Lysine 24 formed alkyl interaction with the drug with a distance of 4.27 Å
- Total 1 pi-alkyl bonds, and 5 hydrogen bonds.

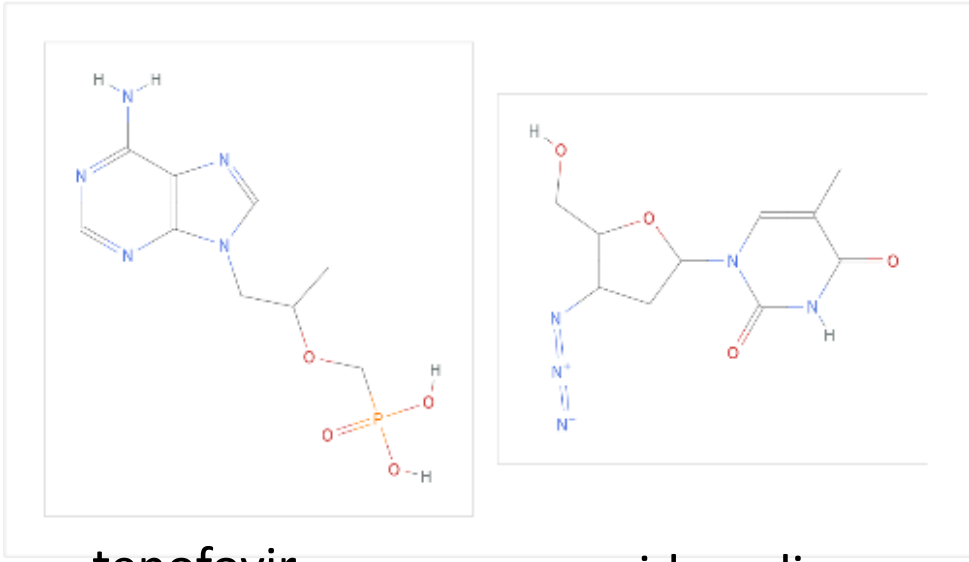


Structural Similarities and Differences

Tenofovir and zidovudine share structural similarities as NRTIs.

However, they have distinct chemical features that influence their binding interactions.

Ligand-binding analysis helps in understanding these differences and optimizing drug design.



tenofovir zidovudine

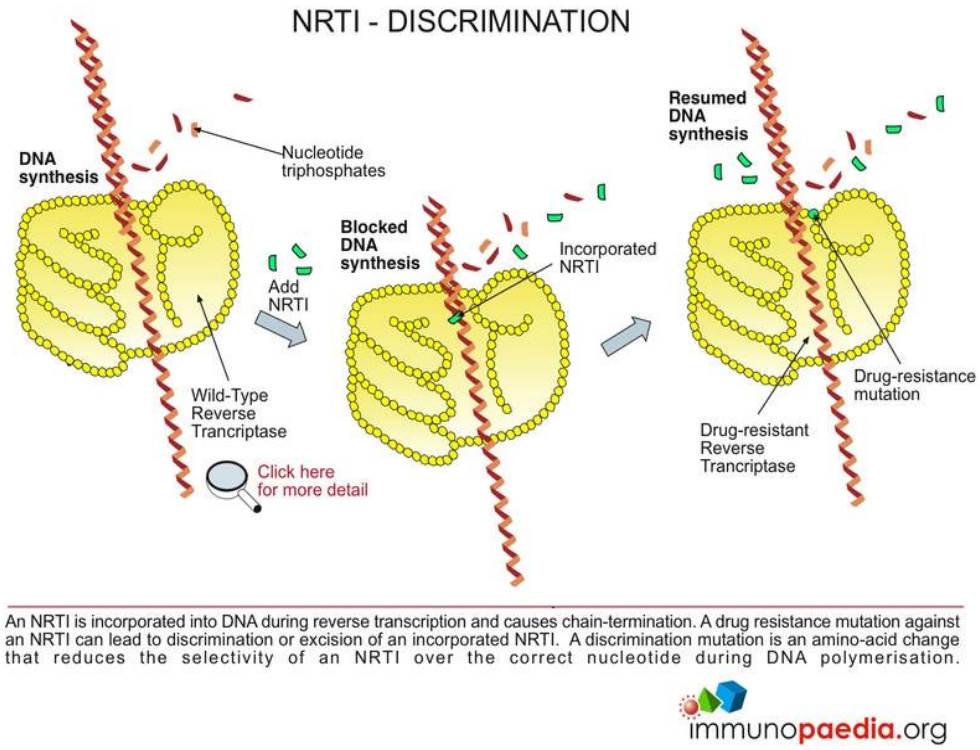
https://pubchem.ncbi.nlm.nih.gov/

Resistance Mechanisms

HIV can develop resistance to reverse transcriptase inhibitors like tenofovir and zidovudine.

Ligand-binding analysis helps in identifying key mutations that confer resistance.

This information guides the development of new drugs or drug combinations to overcome resistance.



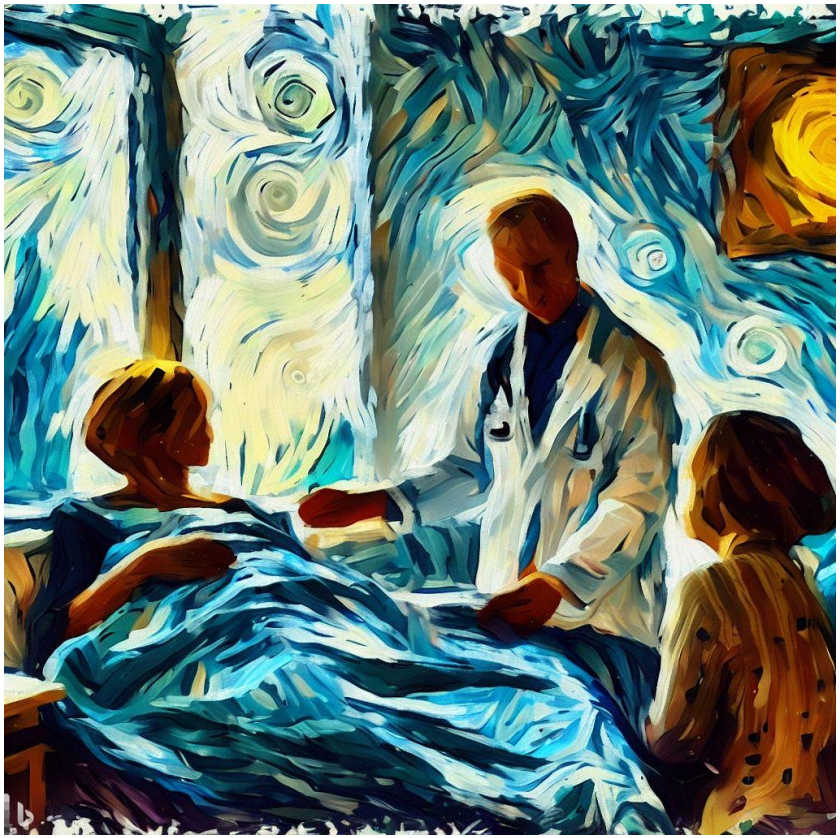
An NRTI is incorporated into DNA during reverse transcription and causes chain-termination. A drug resistance mutation against an NRTI can lead to discrimination or excision of an incorporated NRTI. A discrimination mutation is an amino-acid change that reduces the selectivity of an NRTI over the correct nucleotide during DNA polymerisation.

Clinical Implications

Ligand-binding analysis plays a crucial role in drug development and optimization.

It aids in predicting drug efficacy, safety, and potential drug-drug interactions.

Understanding the binding interactions of tenofovir and zidovudine can improve HIV treatment outcomes.



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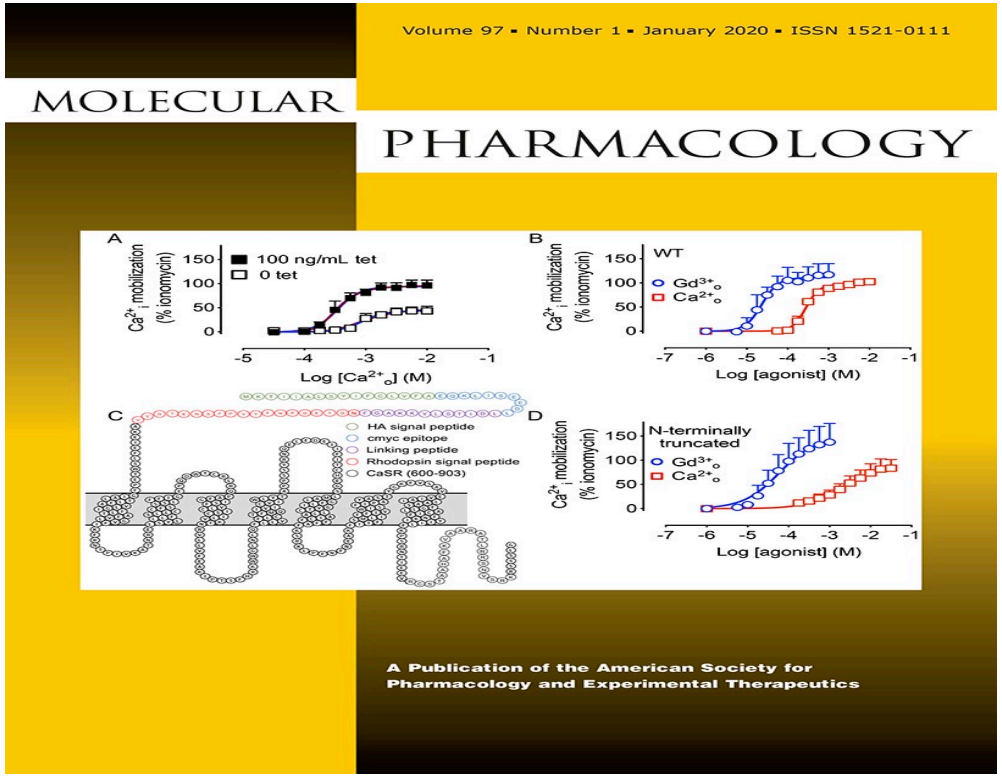
Future Perspectives

Advances in ligand-binding analysis techniques will continue to enhance our understanding of drug-target interactions.

Combination therapies and personalized medicine can be tailored based on ligand-binding analysis data.

Ligand-binding analysis will contribute to the development of novel reverse transcriptase inhibitors and other antiviral drugs.



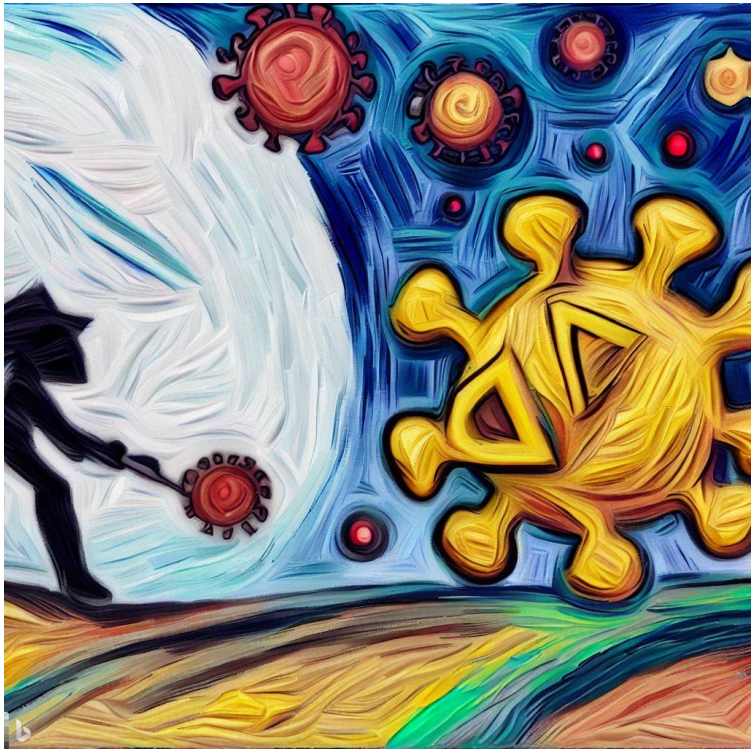
https://molpharm.aspetjournals.org/

Conclusion

Drug ligand-binding analysis provides valuable insights into the interaction between tenofovir, zidovudine, and HIV reverse transcriptase.

The results from molecular docking revealed that tenofovir possessed higher binding affinity with more amino acid binding sites towards HIV-1 RT rather than zidovudine

Ligand-binding analysis is crucial for the development of effective HIV treatment strategies.



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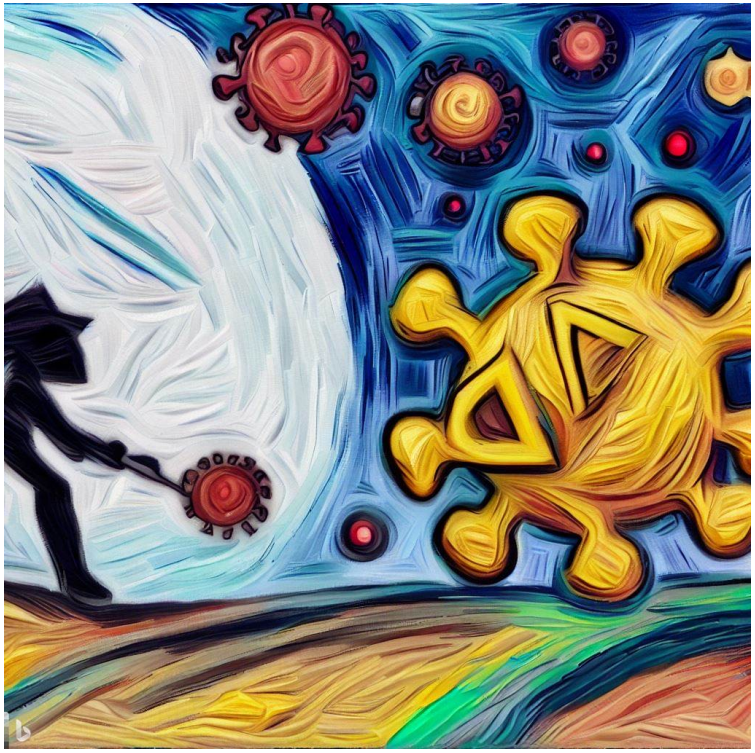
Outlook

- Molecular dynamics simulation is planned for observing the stability of protein-ligand complex
- Will consider other prospective lead compounds to compare with tenofovir and zidovudine



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- Department of Information Technology of i3L
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