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Molecular Docking and Molecular Dynamic Simulation Studies of Zidovudine and Lamivudine against Novel Targets of Human Immunodeficiency Virus

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ABSTRACT

After analyzing multiple pharmaceutical databases like as ScienceDirect, PubMed, Google Scholar, and others, it was found that Zidovudine (ZVD) and Lamivudine (LAM) has not been studied against recently discovered targets such as CC Chemokine Receptor-5 (CCR-5) and HIV-1 capsid protein (HCP). The primary goal of this work was to use *in-silico* techniques to investigate the anti-HIV effects of ZVD and LAM against these two major targets [6Y9Z (Structure of the native full-length HIV-1 capsid protein in complex with Cyclophilin A from helical assembly (-13,9)) and 5UIW (Crystal Structure of CC Chemokine Receptor 5 in complex with high potency HIV entry inhibitor 5P7-CCL5)] using the Schrodinger Software Suite 2021. Moreover, molecular dynamic simulation, prediction of drug-likeliness, bioavailability, and pharmacokinetics of ZVD and LAM, has been explored using online computational tool SwissADME. ZVD demonstrated moderate interactions with all the two targets; CCR-5 (showing Gscore of -4.026 Kcal/mol by forming a hydrogen bond with TYR89 amino acid residue via hydroxyl moiety) and HCP (showing Gscore of -3.631 Kcal/mol by forming two hydrogen bonds with ASN74 and ASN57 amino acid residues via hydroxyl and carbonyl moieties). LAM demonstrated moderate interactions with all the three targets; CCR-5 (showing Gscore of -5.121 Kcal/mol by forming two hydrogen bonds with ASN74 SER180 and THR167 amino acid residues via hydroxyl moiety) and HCP (showing Gscore of -4.004 Kcal/mol by forming a hydrogen bond with ASN57 amino acid residue via amino moiety).

Keywords: Human Immunodeficiency Virus, Zidovudine, Lamivudine, *In silico*, Molecular docking, Pharmacokinetics

1. Introduction

In the latest years, extensive outburst of abundant infectious ailments across the world has created chaos between the populations. Chiefly, the residents in the tropical and sub-tropical areas are concerned by these virulent pathogens. Human immunodeficiency virus (HIV) is a challenge for decades and has affected 40 million people till date [1]. Millions of people lost their lives as the virus targeted the immune system of humans and due to the weakened defense systems against the approaching infections, numerous cancer forms, and other stern clinical

expressions (CD cell count). The major global public health issue impaired the normal functioning of the immune cells and the immunodeficient individual is classified as acquired immunodeficiency syndrome (AIDS) which takes nearly 15 years to develop. Africa and sub-Saharan Africa are the chiefly affected constituency with more than 30 million (60% global infections) HIV affected people individuals [2]. HIV protease is an enzyme of proteolytic nature that plays an imperative role in the formation of structural proteins and enzymes. This homodimer essentially breaks the huge viral protein components that have numerous functions in substrate binding, terminal replication steps, cellular progeny maturation, etc. There are two types of proteases that play functional dominance in the biochemical process. The carbonyl of the amide bond in the scissile bond of the substrate is what the first group of protease enzymes target. The amide hydrolysis of the second type of proteases is initiated by the nucleophilic attack of an amino acid side chain [3].

The products of employing individual compounds stay challenging as a result of resistance to the parent molecule. A great viral population dwells in the body due to an appropriate atmosphere that offers a slighter impediment for development, a huge region for connection, and a superior foundation of sustenance. The attained virulence and encompassed host defense gets frequently aggravated to the "opportunistic" pathogens, which in the due way of time damages the offered performance of the human body. The microscopic pathogens stay over humid, damp, moist, and dark regions of the human body such as hairs, skin, dead tissues, and nails which affects the local population of all sexes and ages, worldwide [4]. In spite of the development of significant elementary acquaintance regarding a variety of pathogens, the existing chemotherapy is still unacceptable as a result of imperfect effectiveness, long-term action, high cost, and unwanted side-effects. These pathogenic microorganisms, particularly those in individuals infected with viruses, are more resistant to treatment, which has further complicated health issues. Consequently, the development of effective and safe antimicrobial medications is essential [5].

ScienceDirect, PubMed, Google Scholar, and other pharmaceutical databases were analysed, it was found that Zidovudine (ZVD) and Lamivudine (LAM) has not been studied against recently discovered targets such as CC Chemokine Receptor 5 and HIV-1 capsid protein. The main purpose of this study was to examine the anti-HIV effects using *in-silico* methods of ZVD and LAM against these two major targets; CC Chemokine Receptor-5 (CCR-5) and HIV-1 capsid protein (HCP). Moreover, molecular dynamic simulation, prediction of drug-likeliness, bioavailability, and pharmacokinetics of ZVD and LAM has been explored using online computational tool SwissADME.

2. Materials and Methods

Molecular Docking

Preparation of ligand

Schrodinger's 2D-sketcher application from their 2021-2 software package was used to design the structures. Maestro version 12.8 was used as the analytical setting for docking. LigPrep was

used to come up with stereoisomers of these ligands. Each ligand was ionised to a target pH of 7.0 in the Epik ioniser up to a maximum of four different postures. To create an optimised low energy 3D ligand, the OPLS 2005 force field was used to produce tautomerized, desalted ligands while preserving the necessary chiralities of the input files [6].

Preparation of protein

Multiple 3D crystalline target structures such as 6Y9Z (Structure of the native full-length HIV-1 capsid protein in complex with Cyclophilin A from helical assembly (-13,9)) and 5UIW (Crystal Structure of CC Chemokine Receptor 5 in complex with high potency HIV entry inhibitor 5P7-CCL5) were obtained from the Protein Data Bank (PDB). The protein structures were created using Maestro 9.1's Protein Preparation Wizard. The pre-processed and inspected structures were taken when developing the biological target. To get the right shape, the disulfide bonds, bond ordering, and formal charges were assigned using the Protein Preparation Wizard module of the Schrodinger Maestro 9.1. Co-factors, metal ions, water molecules in crystal formations beyond a distance of 5 A°, and the hetero group were all removed. The "impref utility" tool was used to optimize hydrogen atoms by keeping all heavy atoms in their original positions, while the "H-bond assignment" tool was used to optimize the hydrogen-bonding network. Molecular docking was used to define the receptor grids for the protein structure, allowing a variety of ligand poses to bind at the anticipated active site. Grids were built and placed at the ligand's centroid in such a way that they covered the whole ligand in a cubic box of defined measurement with the following characteristics: 1.00 Van der Waals scale factor and 0.25 charge cut off. The docking was done in XP mode, and only the energy-minimized postures were scored, which was expressed as a Glide score. The best-docked posture with the lowest Glide score value for each ligand was considered after the highest-scoring ligands were docked [7].

Induced-fit molecular docking (IFD)

Once the structure of the target protein has been determined, the structure-based drug design process may begin again. The low-energy ligands were docked with the rigid receptor, and their fit into the active region and expected binding mechanism were assessed. In receptor-based computational approaches, molecular docking was used to model the ligand's interaction with the macromolecule protein (receptor). IFD calculated that the ligand would make strong contact with the target if the energy levels were low. The procedure is useful for locating conformations with minimal free energy and for eliminating steric clashes entirely. The number of possible postures for each ligand remained at 20 even after applying a 0.7 Van der Waals scaling to the receptor and a 0.5 Van der Waals scaling to the ligand, thereby eliminating side chains and setting an RMSD cutoff of 0.18. Based on the data collected, a subset of compounds was chosen to undergo experimental testing of their biological action. For every ligand, we calculated its Glide Score [8].

Molecular Dynamic (MD) Simulation

The binding stability of the lead chemical in complex with the CCR-5 crystal structure was studied using an MD simulation. The MD simulation [9.10] was done using the Desmond MD programme on an HP Z2 G2 TOWER workstation equipped with an NVIDIA Quadro 6000 4GB GPU and an OPLS-3e force field. The Glide outputs a ligand-protein (LAM-CCR-5) complex, which is then imported into the Maestro module of Schrodinger's programme. The protein-ligand combination was placed in the middle of an orthorhombic box with a minimum of 10 cm of space on all sides. The simulation box was solvated with single point charge (SPC) water molecules, and the necessary counter ions (Na+ and Cl-) were supplied to maintain system equilibrium [11,12]. The 0.15 M NaCl salt content was adjusted using the Desmond System Builder interface to mimic physiological circumstances. By minimising the system energy using the OPLS3e force field over 2000 iterations with a convergence threshold of 1 kcal/mol [13,14], we were able to remove electronic conflict between protein structures. The NPT (Normal pressure and temperature) ensemble was used to run a production MD simulation at 298 K and 1 bar for 1000 steps over 100 ns. The Nose-Hoover Chain thermostat algorithm and the Matrtyna-Tobias-Klein barostat method were used to keep the temperature and pressure stable throughout the simulation [15,16]. Finally, all of the MD trajectory data was fed into Desmond's Simulation Interaction Diagram (SID) to make predictions about the ligand binding orientation and stability.

Pharmacokinetics, bioavailability, and drug-likeliness studies

A pharmacokinetics prediction research was conducted, looking at ADME, bioavailability, and ligand drug-likeness using the SwissADME online programme. Bioavailability radar is computed using the following six physicochemical parameters to identify drug-likeness: lipophilicity, size, polarity, insolubility, flexibility, and insaturation. Passive human gastrointestinal absorption (HIA), blood-brain barrier (BBB) penetration, and permeability glycoprotein (P-gp) substrate/non-substrate status were all found to be positive or negative in the tool's internal BOILED-Egg model. WLOGP is an implementation of a purely atomistic method, XLOGP3 is an atomistic method with corrective factors and a knowledge-based library, and MLOGP is an archetype of topological method relying on free energies of solvation in n-octanol and water calculated by the generalized-born and solvent accessible surface area (GB/SA) model. The Lipinski (Pfizer) filter was the first rule of five to be put into a tool for predicting drug-likeness. Oral bioavailability was predicted using the bioavailability radar, which takes into account a wide range of physicochemical parameters [17].

3. Results and Discussion

Molecular docking

ZVD demonstrated moderate interactions with two targets; CCR-5 (showing Gscore of -4.026 Kcal/mol by forming a hydrogen bond with TYR89 amino acid residue via hydroxyl moiety) and HCP (showing Gscore of -3.631 Kcal/mol by forming two hydrogen bonds with ASN74 and ASN57 amino acid residues via hydroxyl and carbonyl moieties) (**Figure 1**).

A **B**

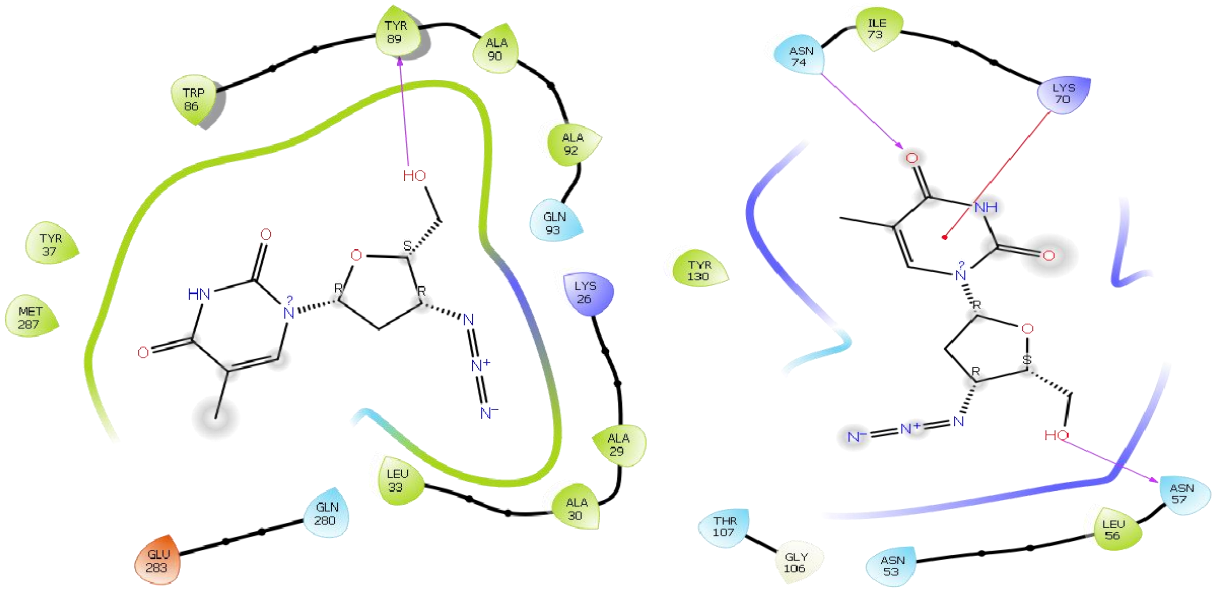

Figure 1. Interaction of Zidovudine with target (A) 5UIW (CC Chemokine Receptor 5) and (B) 6Y9Z (HIV-1 capsid protein).

LAM demonstrated moderate interactions with two targets; CCR-5 (showing Gscore of -5.121 Kcal/mol by forming two hydrogen bonds with ASN74 SER180 and THR167 amino acid residues via hydroxyl moiety) and HCP (showing Gscore of -4.004 Kcal/mol by forming a hydrogen bond with ASN57 amino acid residue via amino moiety) (**Figure 2**). **Table 1** describes the interaction of ZVD and LAM with newer HIV targets.

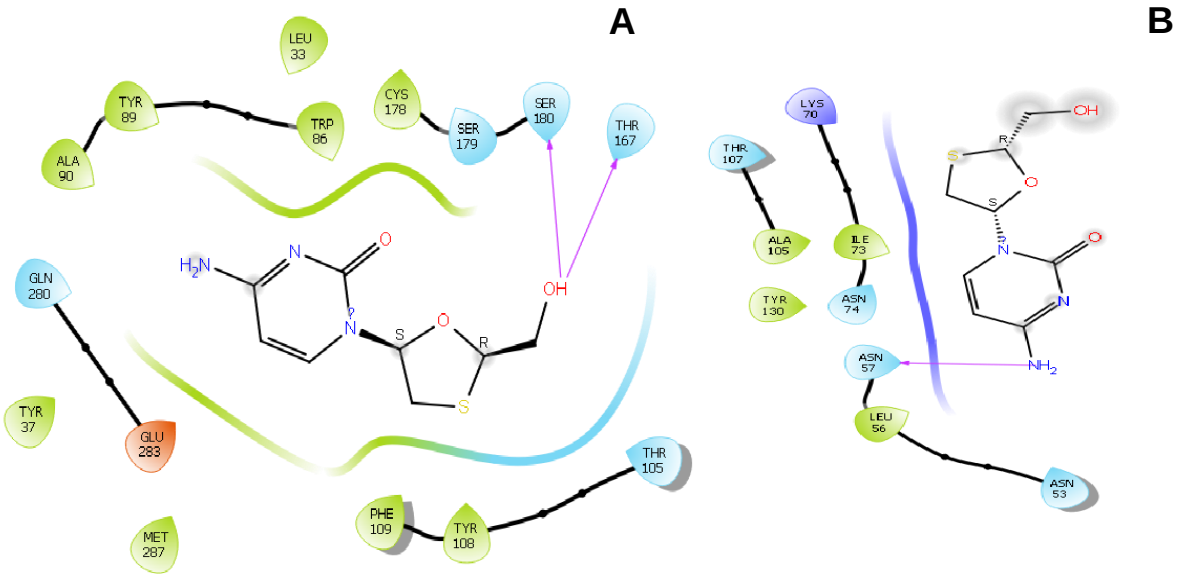

Figure 2. Interaction of Lamivudine with target (A) 5UIW (CC Chemokine Receptor 5) and (B) 6Y9Z (HIV-1 capsid protein).

Table 1. Interaction of Zidovudine and Lamivudine with newer HIV targets.

Specific protein	ZIDOVUDINE				LAMIVUDINE			
	Binding Energy (kcal/mol)	**No. of H Bonds**	**Interacting amino acid residues**	**Non-hydrogen interactions**	**Binding Energy (kcal/mol)**	**No. of H Bonds**	**Interacting amino acid residues**	**Non-hydrogen interactions**
5UIW	-4.026	1	TYR89	-	-5.121	2	SER180, THR167	-
6Y9Z	-3.631	2	ASN74, ASN57	LYS70	-4.004	1	ASN57	-

Molecular Dynamic Simulation

The stability of the bound conformation of LAM inside the binding cavity of CCR-5 was studied using a molecular dynamic simulation to analyse the dynamic behaviour of ligand-protein complex interactions. To learn more about the stability and variability of the LAM-CCR-5 complex conformation, we ran simulations of the systems for up to 100 ns. This study employed a temporal window of 100 ns, which is long enough to identify the configurations of CCR-5 C atoms in combination with LAM.

As can be seen in **Figure 3A**, the stability of the protein-ligand complex was determined using the RMSD values of the protein C atoms. The stability of the protein-ligand combination is predicted to increase as the RMSD decreases throughout the simulation. The stability of the protein-ligand complex, however, decreases as the RMSD increases [18-21]. Minor fluctuations are seen between 82 and 98 ns in the RMSD of the ligands, which originally fluctuated with a value of 1.5 at 3.0 owing to the equilibration. Conversely, RMSD fluctuations in the protein were found to be rather small, spanning 1.6 to 6.4. This shows that LAM is held securely inside the cavity of CCR-5, since the RMSD decreases and maintains very slight variations throughout the course of the simulation duration.

Figure 3B is a graphical representation of the root-mean-square-variation (RMSF) values for each residue throughout the protein backbone. The peaks in these graphs represent the variation in concentration of each amino acid residue during the simulation. Lower RMSF values indicate less residue flexibility and more system stability [22,23], whereas higher RMSF values indicate greater residue flexibility. Secondary structural components, such as -helical and -strand regions, are shown against red and blue backgrounds, respectively, in the RMSF figure, while the loop region is shown against a white backdrop. -helical and -strand regions change less than loop regions because they are often stiffer than the unstructured section of the protein. Since a little amount of conformational change in the active site and main chain is indicative of a stable binding, it follows that the reported lead chemical is securely bound inside the cavity of the target protein binding pocket [24,25]. In the catalytic domain, the RMSF value of protein backbone residues ranges from 0.6 to 2.4, with substantial fluctuations in the C and N-terminal.

LAM was identified to contact with 20 amino acids of the CCR-5, including Pro162(0.9 Å), Ile165(0.8 Å), Phe166(0.8 Å), Arg168(0.8 Å), Ser169(0.8 Å), Gln170(0.8 Å), Gln186(2.4 Å), Tyr187(2.2 Å), Trp190(1.4 Å), Lys191(1.0 Å), Gln194(0.9 Å), Gln8(0.6 Å), Tyr27(1.1 Å), Tyr29(0.9 Å), Thr30(1.0 Å), Ser31(0.8 Å), Gly32(1.0 Å), Cys34(1.1 Å), Ala38(1.1 Å), and Glu66(1.8 Å). The RMSF value of all of these interacting residues is less than 2.4Å, as indicated by the green vertical bars.

2D ligand interaction shows that polar group such as amino and protonated -NH group makes major conventional hydrogen bonding and residue mediated hydrogen bonding. Protein-ligand contract analysis shows that the residues Ile165, Tyr187, and Thr30 show hydrogen interactions with the LAM (**Figure 3C**). During the MD simulation, Ile165, Phe166, and Tyr187 showed major hydrophobic interactions. In this complex one ionic interaction is also visible with protonated -NH group. Water-mediated hydrogen bonding also stabilized the promising LAM in the CCR-5 binding cavity which observe with different residues (**Figure 3D**).

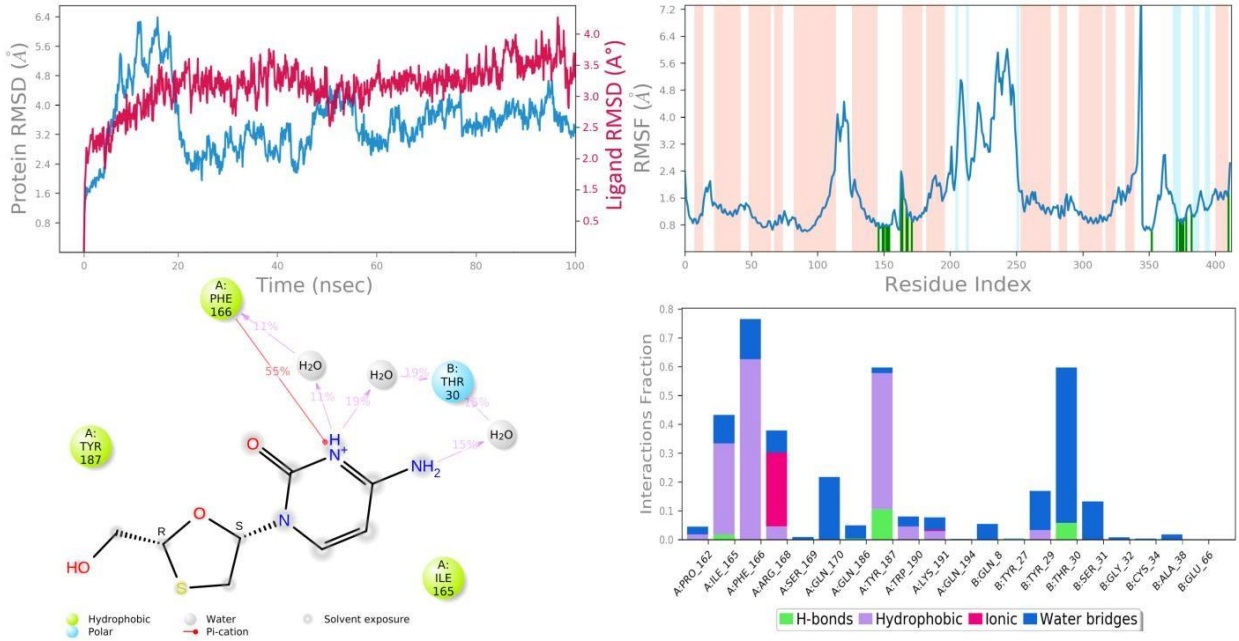

Figure 3. MD simulation analysis of Lamivudine-CCR-5 complex (**A**) RMSD (Protein RMSD is shown in grey while RMSD of Lamivudine are shown in red) (**B**) Protein RMSF (**C**) 2D interaction diagram and (**D**) Protein–ligand contact analysis of MD trajectory.

Pharmacokinetics, bioavailability, and drug-likeliness studies

Data on pharmacokinetics, bioavailability, and similar drugs have predictive values, which are listed in **Table 2**. ZVD absorbed well in the gastrointestinal tract. Poor blood-brain permeability was suggested by a LogP value of 1.93, whereas a more negative value (-7.89 cm/s) was indicative of impaired skin permeation. Neither p-glycoprotein nor cytochrome P450 enzymes 1A2, 2C19, 2C9, 2D6, or 3A4 recognised the chemical as a substrate. Predictions of bioavailability and drug-likeness were somewhat successful (score of 0.55), meeting the

Lipinski's rule of 5 but breaking the Ghose's rule and the Egan's rule. ZVD has been discovered to be very soluble in water. For oral bioavailability prediction (**Figure 4A**), the bioavailability radar indicated the following: INSOLU = insaturation as per Csp3 = 0.60, FLEX = number of rotable bond = 3, SIZE = molecular weight (g/mol) = 267.24 g/mol, POLAR = TPSA (2) = 134.07, and LIPO = XLOGP3 = 0.05 (Figure 4A). ZVD was shown to have little ability to cross the blood-brain barrier in the BOILED-Egg model (**Figure 4B**), but to have great ability to cross the gastrointestinal absorption barrier. PGP positivity as a non-substrate was found in the model proposed for this molecule. For the computer prediction of small molecule lipophilicity and polarity, the Brain Or IntestinaL EstimateD permeation technique (BOILED-Egg) has been proposed as a reliable predictive model. The BOILED-Egg diagram and the bioavailability radar suggest that the chemical is a rather good drug candidate. These predictive results for HIV therapy should be confirmed using functional and pharmacological assessments both in vitro and in vivo.

The rate of GIT absorption was rather high for LAM. A negative LogP result (-8.36 cm/s) was indicative of reduced skin permeation, while a low LogP value (1.04 cm/s) revealed inadequate blood-brain permeability. Neither p-glycoprotein nor cytochrome P450 enzymes 1A2, 2C19, 2C9, 2D6, nor 3A4 recognised the chemical as a substrate. Predictions of bioavailability and drug-likeness were only somewhat accurate (0.55 out of 1.00; met Lipinski's rule of 5, but failed Ghose's criterion). It was discovered that LAM has a high solubility in water. If you look at Figure 5A of the bioavailability radar, you can see that the target value for INSATU = insaturation according to Csp3 is 0.50, the number of rotatable bonds is 2, INSOLU Logs (ESOL) is -0.84 (soluble), the molecular weight is 229.26 g/mol, the polarity index is 115.67, the size is 229.26 g/mol, and the lipophilicity index is 0. The BOILED-Egg model (Figure 5B) showed that although LAM is unable to cross the blood-brain barrier, it is well absorbed in the intestines. PGP positivity as a non-substrate was found in the model proposed for this molecule. For the computer prediction of small molecule lipophilicity and polarity, the Brain Or IntestinaL EstimateD permeation technique (BOILED-Egg) has been proposed as a reliable predictive model. The BOILED-Egg diagram and the bioavailability radar suggest that the chemical is a rather good drug candidate. These predictive results for HIV therapy should be confirmed using functional and pharmacological assessments both *in vitro* and *in vivo*.

Table 2. Pharmacokinetics, bioavailability, and drug-likeness properties of Zidovudine and Lamivudine.

PROPERTIES	ZIDOVUDINE	LAMIVUDINE
Physicochemical Properties		
Formula	$C_{10}H_{13}N_5O_4$	$C_8H_{11}N_3O_3S$
Molecular weight (g/mol)	267.24	229.26
Number of heavy atoms	19	15
Number of aromatic heavy atoms	6	6
Fraction Csp3	0.60	0.50
Number of rotatable bonds	3	2

Number of H-bond acceptors	7	4
Number of H-bond donors	2	2
Molar Refractivity	61.73	56.31
TPSA (A^2)	134.07	115.67
Lipophilicity		
Log Po/w (iLOGP)	1.93	1.04
Log Po/w (XLOGP3)	0.05	-0.93
Log Po/w (WLOGP)	-0.52	-0.91
Log Po/w (MLOGP)	-1.25	-1.02
Log Po/w (SILICOS-IT)	-0.78	-0.47
Consensus Log Po/w	-0.11	-0.46
Water Solubility		
Log S (ESOL)	-1.56	-0.84
Solubility (mg/ml ; mol/l)	7.29e+00 ; 2.73e-02	3.32e+01 ; 1.45e-01
Class	Very soluble	Very soluble
Log S (Ali)	-2.42	-1.02
Solubility (mg/ml ; mol/l)	1.02e+00 ; 3.81e-03	2.21e+01 ; 9.66e-02
Class	Soluble	Very soluble
Log S (SILICOS-IT)	-1.16	-0.43
Solubility (mg/ml ; mol/l)	1.84e-01; 6.87e-02	8.46e+01; 3.69e-01
Class	Soluble	Soluble
Pharmacokinetics		
GI absorption	High	High
BBB permeant	No	No
P-gp substrate	No	No
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Log Kp (skin permeation) (cm/s)	-7.89	-8.36
Drug-likeness		
Lipinski	Yes; 0 violation	Yes; 0 violation
Ghose	No; 1 violation: WLOGP<-0.4	No; 1 violation: WLOGP<-0.4
Veber	Yes	Yes
Egan	No; 1 violation: TPSA>131.6	Yes
Muegge	Yes	Yes
Bioavailability Score	0.55	0.55
Medicinal Chemistry		
PAINS	1 alert: azo_A	0 alert
Brenk	3 alerts: azido_group, diazo_group, quaternary_nitrogen_3	0 alert

Lead-likeness	Yes	No; 1 violation: MW<250
Synthetic accessibility	3.93	3.57

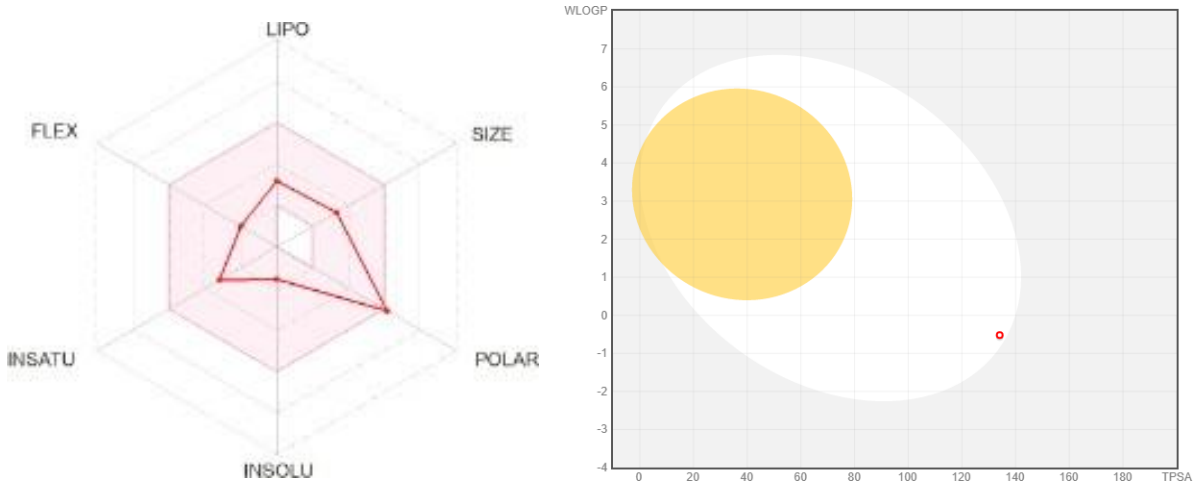

Figure 4. Zidovudine characteristics: (A) Bioavailability radar plot, (B) BOILED-Egg representation.

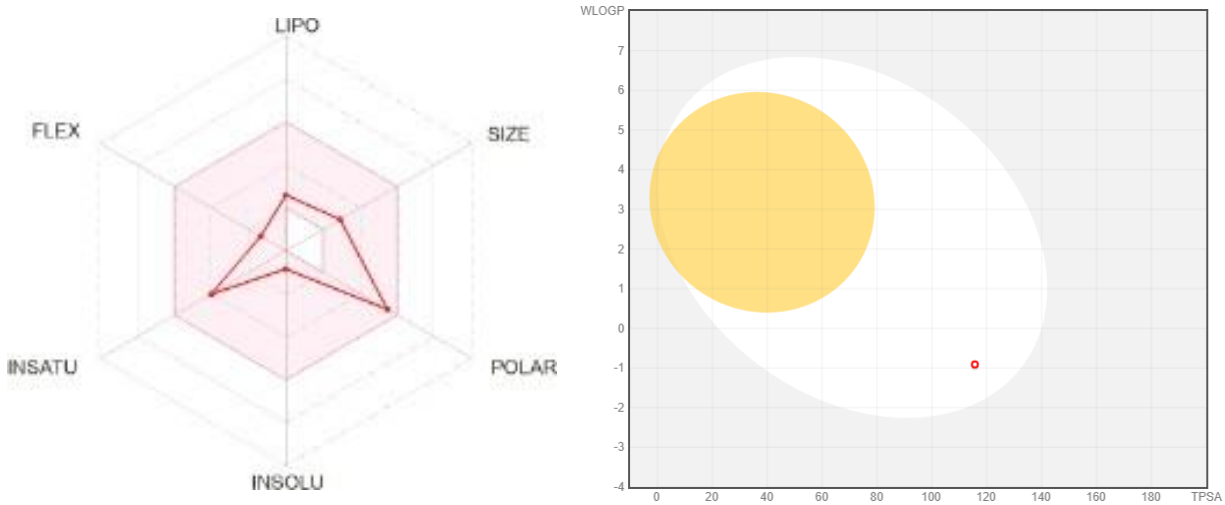

Figure 5. Lamivudine characteristics: (A) Bioavailability radar plot, (B) BOILED-Egg representation.

4. Conclusion

By directing researchers to investigate zidovudine and lamivudine against two critical targets (CCR-5 and HCP), this *in silico* study cleared the way for the creation of novel anti-retroviral medicines, which play a vital role in managing HIV-AIDS. These inhibitors demonstrated that the formation of hydrogen bonds (via the -OH, -NH, etc. groups), Van der Waals forces, hydrophobic interaction, and electrostatic forces, all contribute to the stabilization of the ligand-receptor complex and enable deeper penetration into the active site cavity of the receptors. The drugs' pharmacokinetic and bioavailability properties allowed for their successful approval. More

pharmacotherapeutic alternatives and openings in the academic and scientific communities would result from a solution to the perennial problem of improving synthetic chemicals' anti-retroviral effects.

Conflict of Interest

The authors declare no conflict of interest.

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5. References

1. Mahapatra DK, Bharti SK, Asati V. Chalcone scaffolds as anti-infective agents: Structural and molecular target perspectives. Eur J Med Chem. 2015;101:496-524.
2. Mahapatra DK, Bharti SK, Asati V. Recent Advancements in the Pharmacotherapeutic Perspectives of Some Chalcone Scaffold Containing Natural Compounds as Potential Anti-Virals. InNatural Products Pharmacology and Phytochemicals for Health Care 2021 (pp. 117-131). Apple Academic Press.
3. Mahapatra DK, Bharti SK. Medicinal Chemistry with Pharmaceutical Product Development. CRC Press; 2019.
4. Mahapatra DK, Bharti SK. Handbook of Research on Medicinal Chemistry: Innovations and Methodologies. Taylor & Francis; 2017.
5. Pandey R, Dubey I, Ahmad I, Mahapatra DK, Patel H, Kumar P. In silico Study of Some Dexamethasone Analogs and Derivatives against SARs-CoV-2 Target: A Cost-effective Alternative to Remdesivir for Various COVID Phases. Curr Chin Sci. 2022;2(4):294-309.
6. Asati V, Bharti SK, Rathore A, Mahapatra DK. SWFB and GA strategies for variable selection in QSAR studies for the validation of thiazolidine-2, 4-dione derivatives as promising antitumor candidates. Indian J Pharm Educ Res. 2017;51(3):436-51.
7. Chhajed SS, Chaskar S, Kshirsagar SK, Haldar GA, Mahapatra DK. Rational design and synthesis of some PPAR-γ agonists: Substituted benzylideneamino-benzylidene-thiazolidine-2, 4-diones. Comp Biol Chem. 2017;67:260-5.
8. Mahapatra DK, Das D, Shivhare RS. Substituted thiazole linked murrayanine-Schiff's base derivatives as potential anti-breast cancer candidates: Future EGFR Kinase inhibitors. Int J Pharm Sci Drug Res. 2017;9(3):139-44.
9. D. E. Shaw Research, Schrödinger Release (2020-3). Desmond molecular dynamics system. Maestro-Desmond interoperability tools.

10. H. A. Radwan, I. Ahmad, I. M. Othman, M. A. Gad-Elkareem, H. Patel, K. Aouadi, M. Snoussi, A. Kadri, Design, synthesis, in vitro anticancer and antimicrobial evaluation, SAR analysis, molecular docking and dynamic simulation of new pyrazoles, triazoles and pyridazines based isoxazole. J. Mol. Struct. 16 (2022) 133312.

11. Iqrar Ahmad, Rahul Pawara, Harun Patel, In silico toxicity investigation of Methaqualone's conjunctival, retinal, and gastrointestinal haemorrhage by molecular modelling Approach. https://doi.org/10.1080/08927022.2022.2113412

12. Chaudhari B, Patel H, Thakar S, Ahmad I, Bansode D. Optimizing the Sunitinib for cardio-toxicity and thyro-toxicity by scaffold hopping approach. In Silico Pharmacol. 2022 Jul 2;10(1):10. doi: 10.1007/s40203-022-00125-1.

13. M. M. Farhan, M. A. Guma, M. A. Rabeea, I. Ahmad, H. Patel, Synthesizes, Characterization, Molecular docking and in vitro Bioactivity study of new compounds containing Triple Beta Lactam Rings. J. Mol. Struct. 23 (2022) 133781.

14. D. Osmaniye, Ş. Karaca, B. Kurban, M. Baysal, I. Ahmad, H. Patel, Y. Özkay, Z. Asım Kaplancıklı, Design, synthesis, molecular docking and molecular dynamics studies of novel triazolothiadiazine derivatives containing furan or thiophene rings as anticancer agents. Bio. Org. Chem. (2022) 122:105709.

15. NC Desai, SB Joshi, AG Khasiya, DJ Jadeja, HK Mehta, Pyrazolo-Imidazolidinones: Synthesis, Antimicrobial Assessment and Molecular Modelling Studies by Molecular Mechanic and Quantum Mechanic Approach Journal of Molecular Structure 1270 (2022) 134000.

16. Rakesh Kumar Paul, Iqrar Ahmad Harun Patel, Vipin Kumar, Kaisar Raza, Phytochemicals from Amberboa ramosa as potential DPP-IV inhibitors for the management of Type-II Diabetes Mellitus: Inferences from In-silico Investigations, , Journal of Molecular Structure, 2022, 134045.

17. Singh RK, Mishra AK, Kumar P, Mahapatra DK. Molecular Docking and In Vivo Screening of Some Bioactive Phenoxyacetanilide Derivatives as Potent Non-Steroidal Anti-Inflammatory Drugs. Int J Cur Res Rev. 2021;13(10):189-196.

18. U. Acar Çevik, I. Celik, A. Işık, I. Ahmad, H. Patel, Y. Özkay, Z. A. Kaplancıklı, Design, synthesis, molecular modeling, DFT, ADME and biological evaluation studies of some new 1,3,4-oxadiazole linked benzimidazoles as anticancer agents and aromatase inhibitors. J. Biomol. Struct. Dyn. (2022) 1–15.

19. Boulaamane, Y., Ahmad, I., Patel, H., Das, N., Britel, M. R., & Maurady, A. (2022). Structural exploration of selected C6 and C7-substituted coumarin isomers as selective MAO-B inhibitors. Journal of Biomolecular Structure and Dynamics, 1-15.

20. Abdelgawad, Mohamed A., et al. "Development of bromo-and fluoro-based α, β-unsaturated ketones as highly potent MAO-B inhibitors for the treatment of Parkinson's disease." Journal of Molecular Structure 1266 (2022): 133545.

21. Manesh S.Tople Navin B. Patel Parth P.Patel Amit kumar Purohit Iqrar Ahmad, Harun Patel, An in silico-in vitro antimalarial and antimicrobial investigation of newer 7-Chloroquinoline based Schiff-bases, Journal of Molecular Structure, 134016.

22. Ayipo, Y.O., Alananzeh, W.A., Ahmad, I., Patel, H. and Mordi, M.N., 2022. Structural modelling and in silico pharmacology of β-carboline alkaloids as potent 5-HT1A receptor antagonists and reuptake inhibitors. Journal of Biomolecular Structure and Dynamics, pp.1-17.

23. I. Ahmad, R. H. Pawara, R. T, Girase, A. Y. Pathan, V. R. Jagatap, N. Desai, Y. O. Ayipo, S. J. Surana, H. Patel, Synthesis, Molecular Modeling Study, and Quantum-Chemical-Based Investigations of Isoindoline-1,3-diones as Antimycobacterial Agents. ACS Omega. (2022) 10;7(25):21820-21844.

24. K. K. Bharadwaj, I. Ahmad, S. Pati, A. Ghosh, T. Sarkar, B. Rabha, H. Patel, D. Baishya, H. A. Edinur, Z. Abdul Kari, M. R. Ahmad Mohd Zain, W. I. Wan Rosli, Potent Bioactive Compounds from Seaweed Waste to Combat Cancer Through Bioinformatics Investigation. Front. nutr. 9, (2022) 889276.

25. Manel Ben Hammouda, Iqrar Ahmad, Assia Hamdi, Amal Dbeibia, Harun Patel, Nouha Bouali, Walid Sabri Hamadou, Karim Hosni, Siwar Ghannay, Fahad Alminderej, Emira Noumi, Mejdi Snoussi, Kaïss Aouadi, Adel Kadri, Design, synthesis, biological evaluation and in silico studies of novel 1,2,3-triazole linked benzoxazine-2,4-dione conjugates as potent antimicrobial, antioxidant and anti-inflammatory agents, , Arabian Journal of Chemistry 2022, 104226.