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Research Article

Integrated *In Silico* Approach for Identification of a Lead Compound Targeting HIV-1 Reverse Transcriptase

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ABSTRACT

Human Immunodeficiency Virus type-1 (HIV-1) reverse transcriptase (RT) remains a critical therapeutic target for antiretroviral drug development. In this study, a ligand-based pharmacophore modeling approach was employed using Nevirapine as the reference compound to identify potential RT inhibitors. The pharmacophore model was constructed and used for virtual screening via Pharmit, followed by similarity-based retrieval of compounds from the ZINC Database, yielding 57 candidate molecules. Drug-likeness evaluation using Lipinski's rule of five resulted in 47 compounds passing the criteria. Further ADMET profiling using ADMETlab 3.0 significantly narrowed the pool, with only one compound satisfying stringent pharmacokinetic and toxicity parameters. Molecular docking analysis was then performed against HIV-1 RT to validate binding affinity. The reference drug Nevirapine exhibited a binding energy of −6.0 kcal/mol, whereas the identified lead compound demonstrated a comparatively improved binding energy of −6.6 kcal/mol. These findings suggest that the screened lead compound possesses favorable binding potential and acceptable pharmacokinetic properties, warranting further investigation. This study highlights the effectiveness of an integrated pharmacophore-based virtual screening and ADMET-guided filtering approach in identifying potential HIV-1 RT inhibitors.

1. Introduction

Human Immunodeficiency Virus Type-1 remains a significant global health challenge despite major advances in antiretroviral therapy. The virus continues to evolve through rapid mutation, leading to drug resistance and reduced therapeutic efficacy. Among the viral enzymes, HIV-1 Reverse Transcriptase plays a crucial role by catalyzing the conversion of viral RNA into DNA, enabling its integration into the host genome (Sanober & Mamidala, 2024). Due to its essential function in the viral life cycle, reverse transcriptase has been widely recognized as a validated target for antiviral drug development.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as Nevirapine, have been extensively used in HIV treatment. These inhibitors act by binding to an allosteric site of the enzyme, inducing conformational changes that inhibit its activity (Annan et al., 2024). However, the emergence of resistant viral strains and adverse effects has limited their long-term clinical effectiveness. Therefore, there is a continuous need to identify novel inhibitors with improved binding efficiency, reduced toxicity, and better pharmacokinetic properties.

In recent years, computational approaches such as pharmacophore modeling, virtual screening, and ADMET prediction have gained prominence in drug discovery. Ligand-based pharmacophore modeling enables the identification of key molecular features required for biological activity, facilitating the screening of large compound libraries. When integrated with drug-likeness and ADMET evaluation, these methods provide a rational framework for prioritizing potential lead compounds. The present study employs an integrated in silico strategy to identify novel inhibitors targeting HIV-1 Reverse Transcriptase

Materials and Methods

2.1. Pharmacophore Generation and Virtual Screening

A ligand-based pharmacophore modeling approach was employed using Nevirapine as the template to identify essential molecular features required for inhibition of HIV-1 Reverse Transcriptase. The pharmacophore model was constructed by mapping key interaction features such as hydrogen bond donors, hydrogen bond acceptors, hydrophobic regions, and aromatic moieties (Giordano et al., 2022). The generated model

was validated and subsequently utilized for virtual screening using the Pharmit platform against a subset of the ZINC Database. This screening process resulted in the identification of 57 candidate compounds that satisfied the defined pharmacophoric features.

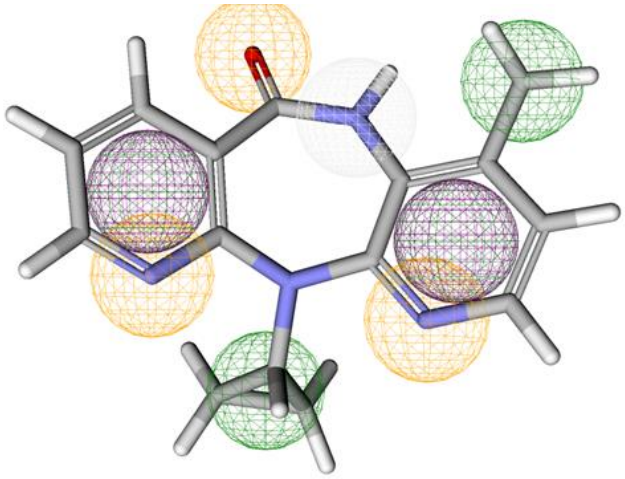

Figure-1. Pharmacophore modelling of Nevirapine (NVP)

2.2 Drug-Likeness Evaluation (Lipinski's Rule of Five)

The screened compounds were subjected to drug-likeness evaluation using Lipinski's Rule of Five to assess their suitability for oral bioavailability. This rule evaluates critical physicochemical parameters including molecular weight, lipophilicity (LogP), hydrogen bond donors, and hydrogen bond acceptors. Compounds that satisfied these criteria are considered more likely to exhibit favorable absorption and permeability characteristics (Shiri et al., 2018). In this study, out of the 57 screened compounds, 47 compounds met the Lipinski criteria and were selected for further analysis.

2.3 ADMET Analysis

The compounds that passed Lipinski filtering were further evaluated for pharmacokinetic and toxicity properties using ADMET analysis. ADMET profiling was performed using ADMETlab 3.0 to predict absorption, distribution, metabolism, excretion, and toxicity parameters (Wan et al., 2018). This step is crucial for determining the biological suitability and safety of the compounds. Stringent ADMET filtering significantly reduced the number of potential candidates, and only one compound was found to possess an optimal balance of pharmacokinetic properties and minimal predicted toxicity (Sanober & Mamidala, 2026).

2.4 Molecular docking analysis

2.4.1 Protein Preparation

The three-dimensional crystal structure of HIV-1 Reverse Transcriptase (PDB ID: 1JLB) was retrieved from the RCSB Protein Data Bank in PDB format. Protein preparation was performed using AutoDock Tools (ADT) (Morris et al., 2009), where the protein structure was cleaned by removing crystallographic water molecules and other unwanted heteroatoms. Polar hydrogen atoms were added, Kollman charges were assigned, and the prepared protein structure was subsequently converted into PDBQT format for molecular docking studies (Sanober & Mamidala, 2025).

2.4.2 Ligand Preparation

The selected lead compound was retrieved from the ZINC Database in SDF format. The ligand structure was converted into PDB format using Open Babel software. Further ligand optimization, including the addition of Gasteiger charges and assignment of rotatable bonds, was carried out using Auto Dock Tools, after which the ligand was saved in PDBQT format for docking analysis (Sanober & Mamidala, 2024).

2.4.3 Molecular Docking Using AutoDock Vina

Molecular docking analysis was performed using AutoDock Vina to evaluate the binding affinity of the lead compound against HIV-1 Reverse Transcriptase. The docking grid box was centered at coordinates X = −16.444, Y = 130.161, and Z = 180.249, with dimensions of 112 Å × 126 Å × 106 Å to adequately encompass the active binding region of the target protein. Docking simulations were conducted using an energy range of 4 kcal/mol and 10 binding modes (num_modes = 10) to generate multiple ligand conformations within the binding pocket.

The docked conformations were ranked based on binding affinity, and the best binding pose was selected according to the lowest binding energy value. Protein–ligand interactions were subsequently analyzed to determine hydrogen bonding, hydrophobic interactions, and amino acid residues involved in ligand stabilization within the active site.Antigenicity and allergenicity of the identified conserved regions were determined as follows. VaxiJen tool was used to identify immunoprotective sequences based on identifying such sequences from bacterial, viral, tumour, fungi and parasite antigens and calculating their auto-cross covariance values [11]. The threshold for viral models was 0.4 (default value); sequences that scored equal to or below 0.4 were considered non-antigenic, and those that scored above were considered antigenic. The Immune Epitope Database (IEDB) tools were used to find possible T-cell and B-cell epitopes in conserved protein sequences. From the input sequence, it identifies the string most likely to have immunogenicity and assigns a score of likelihood [12]. The NetCTL 1.2 tool was used to identify CTL epitopes in the amino acid sequences of SARS-CoV-2. It supports 12 MHC class 1 supertypes [13]. The allergenicity of the amino acid sequences was identified using the AllerTOP tool. Only those sequences with no allergenic effects were used for further analysis [14].

The conserved antigenic and non-allergenic epitopes were then mapped onto the respective crystal structure of the proteins as follows. Experimentally determined structures of non-structural proteins (NSPs) and structural proteins of SARS-CoV-2 were retrieved from the RSCB Protein Data Bank (PDB) [15]. The structure of conserved peptide sequences was visualised in PyMOL v2.4.1 [16]. The structures of NSP-4 and NSP-6 were predicted using the Alphafold2 v2.1.1, which uses a machine learning approach for modelling even without homologous structures [17]. The best model was selected from the five predicted structures based on the predicted local distance difference test (PLDDT) score. Further, the model was evaluated using the PROCHECK [18] and ERRAT [19] modules of the SAVES v6.0 server to validate the stereochemistry and overall quality factors. The loop regions of the predicted models were refined using the ModLoop server [18] and validated using the SAVES server. Modelled structures were analysed using PyMOL.

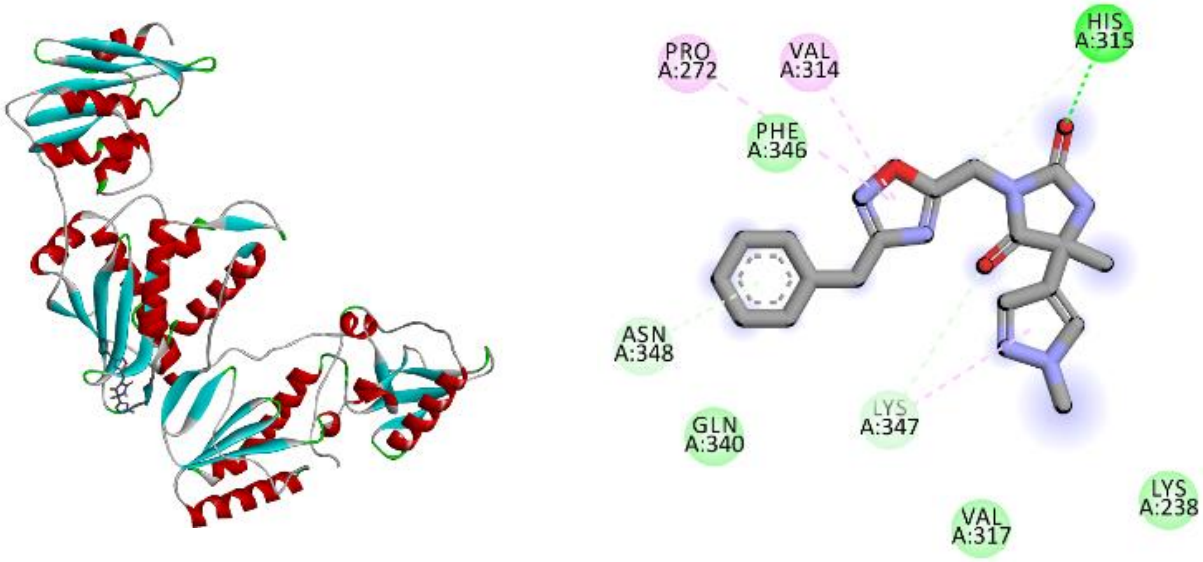

Figure- 2. 3D and 2D Molecular docking interaction of ligand ZINC89917129 with HIV-1 Reverse Transcriptase Enzyme (PDB ID: 1JLB)

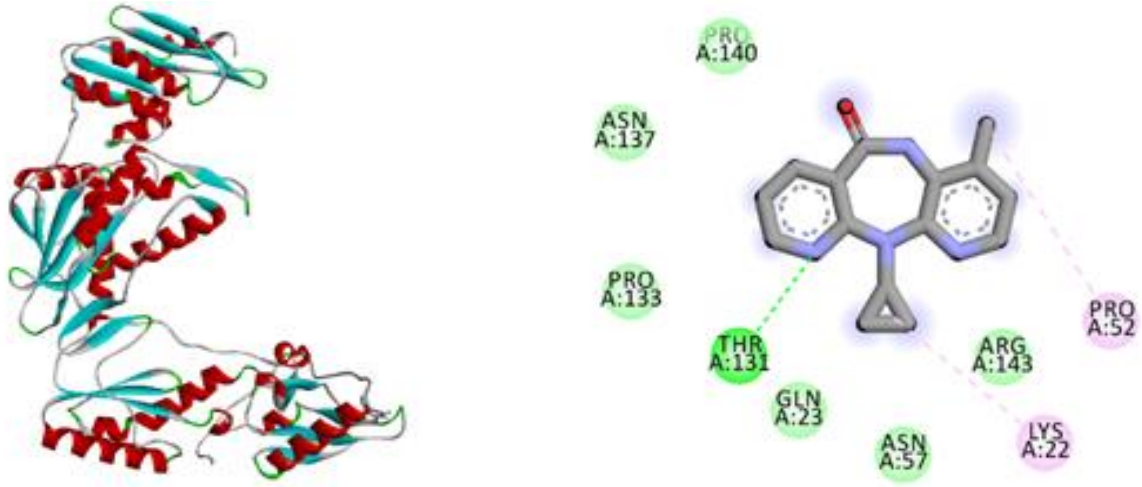

Figure-3. 3D and 2D Molecular docking interaction of ligand Nevirapine with HIV-1 Reverse Transcriptase Enzyme (PDB ID: 1JLB)

3. Results and Discussion

3.1. Pharmacophore Screening, Drug-Likeness and ADMET Evaluation

The ligand-based pharmacophore screening approach employing Nevirapine as the reference inhibitor successfully identified 57 candidate compounds from the ZINC Database possessing structural and chemical features complementary to the pharmacophoric model. These screened compounds were subjected to drug-likeness evaluation based on Lipinski's Rule of Five to assess their suitability as orally active drug candidates. Among the identified molecules, 47 compounds satisfied the Lipinski criteria, indicating favorable physicochemical properties and potential oral bioavailability (Table 1). Subsequent ADMET profiling was performed using ADMETlab 3.0 to evaluate the pharmacokinetic and toxicity characteristics of the screened compounds. Stringent filtering based on absorption, distribution, metabolism, excretion, and toxicity parameters significantly reduced the candidate pool, resulting in the identification of a single compound, ZINC89917129, which demonstrated optimal pharmacokinetic behavior and minimal predicted toxicity.

3.2 Molecular Docking Analysis

To further validate the inhibitory potential of the selected lead compound, molecular docking analysis was conducted against HIV-1 Reverse Transcriptase using AutoDock Vina. The docking results revealed that the standard reference drug Nevirapine exhibited a binding affinity of −6.0 kcal/mol, whereas the identified lead compound ZINC89917129 demonstrated a comparatively enhanced binding affinity of −6.6 kcal/mol (Table 2).

Interaction analysis indicated that the lead compound formed stable interactions within the active site of HIV-1 Reverse Transcriptase, suggesting favorable accommodation within the binding pocket and effective molecular recognition by the target receptor (Fig. 2 and Fig. 3). The improved binding affinity of the lead compound relative to the standard drug indicates its potential as a promising inhibitor of HIV-1 Reverse Transcriptase.

Table 1. Drug-likeness evaluation of screened compounds based on Lipinski's Rule of Five

S.NO	ZINC ID	MW	LOGP	NHD	NHA	TPSA
1.	ZINC72307036	432.11	2.3	1	9	103.41
2.	ZINC58167131	431.1	2.0	1	10	120.73
3.	ZINC1660724741	403.17	2.6	1	8	102.91
4.	ZINC1875335723	410.1	1.1	2	8	101.8
5.	ZINC9254042	427.07	4.0	1	6	72.7
6.	ZINC823033463	297.13	0.6	1	7	81.81
7.	ZINC1875324976	381.15	-0.3	2	10	127.82
8.	ZINC1875324976	381.15	-0.3	2	10	127.82
9.	ZINC1875324976	381.15	-0.3	2	10	127.82
10.	ZINC32932461	395.09	2.7	2	6	83.56
11.	ZINC70655942	395.12	3.0	1	9	107.59
12.	ZINC1364796562	343.07	1.8	1	7	90.41
13.	ZINC34510479	281.13	1.1	3	6	84.14
14.	ZINC20745479	322.14	1.3	1	6	76.88
15.	ZINC1875333274	329.09	1.5	1	7	89.77
16.	ZINC1875333274	329.09	1.5	1	7	89.77
17.	ZINC1875335723	410.1	1.1	2	8	101.8
18.	ZINC4778	266.12	1.2	1	5	58.12
19.	ZINC670455488	313.12	0.9	1	8	102.91
20.	ZINC534584175	312.09	1.6	1	8	111.12
21.	ZINC2100477057	366.12	2.2	1	8	98.21
22.	ZINC12201386	341.13	2.0	1	6	72.7
23.	ZINC823032990	311.14	0.9	1	7	81.81
24.	ZINC823032990	311.14	0.9	1	7	81.81
25.	ZINC39026528	311.1	1.2	1	8	101.26
26.	ZINC39026528	311.1	1.2	1	8	101.26
27.	ZINC225808845	438.18	2.7	1	8	85.17
28.	ZINC225808845	438.18	2.7	1	8	85.17
29.	ZINC65742688	294.11	1.0	1	6	75.19
30.	ZINC5842178	254.12	1.3	1	5	58.12
31.	ZINC89917131	366.14	1.8	1	9	106.15
32.	ZINC65740769	292.13	1.8	1	5	58.12
33.	ZINC333188518	376.13	1.2	1	9	103.41
34.	ZINC333188518	376.13	1.2	1	9	103.41
35.	ZINC333188516	376.13	1.2	1	9	103.41
36.	ZINC333188518	376.13	1.2	1	9	103.41
37.	ZINC66916780	285.09	0.3	1	8	102.91
38.	ZINC670457959	365.13	0.6	1	10	116.82
39.	ZINC670457959	365.13	0.6	1	10	116.82
40.	ZINC56901023	393.09	2.7	1	8	99
41.	ZINC96427821	339.17	1.3	1	7	81.81
42.	ZINC670461883	327.14	1.6	1	8	102.91
43.	ZINC670461882	327.14	1.6	1	8	102.91
44.	ZINC65742963	282.11	1.4	2	6	78.35
45.	ZINC39177731	344.03	3.0	1	5	58.12
46.	ZINC1565555244	337.15	1.3	1	7	85.84
47.	ZINC1614936741	337.15	1.3	1	7	85.84

Identified compound ZINC89917129 exhibited a balanced profile of favorable binding affinity, acceptable drug-likeness, and promising ADMET characteristics, highlighting its potential as a lead candidate for further optimization and experimental validation in anti-HIV drug development

4. Conclusion

The present study employed an integrated in silico drug discovery approach combining ligand-based pharmacophore modeling, virtual screening, drug-likeness assessment, ADMET profiling, and molecular docking to identify potential inhibitors targeting HIV-1 Reverse Transcriptase. Pharmacophore-based screening using Nevirapine as the r eference ligand identified 57 candidate compounds from the ZINC Database, of which 47 compounds satisfied Lipinski's Rule of Five. Further pharmacokinetic and toxicity evaluation through ADMET analysis narrowed the screened compounds to a single lead candidate, ZINC89917129, exhibiting favorable drug-like and safety profiles. Molecular docking studies demonstrated that ZINC89917129 showed a slightly improved binding affinity (−6.6 kcal/mol) compared to the reference drug Nevirapine (−6.0 kcal/mol) and formed stable interactions within the active site of HIV-1 Reverse Transcriptase. Collectively, these findings suggest that ZINC89917129 may serve as a promising lead

scaffold for the development of novel HIV-1 Reverse Transcriptase inhibitors.

Competing interests:

The authors declare that they have no competing interests

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