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In silico ADME, Bioactivity, Toxicity Predictions and Molecular Docking studies of a few Antiviral Agents

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ABSTRACT

Computer-aided drug design methodologies have emerged as pivotal tools in modern drug discovery, offering significant cost savings and time efficiency. Analysis of the physicochemical properties, bioactivity, and toxicity profiles of existing drugs enables the researchers to identifythe pharmacophore prerequisites crucial for designing novel compounds targeting specific biological targets. In the present work, 15 antiviral drugs, which have been approved by US FDA (since 2000) were selected for the computational studies. The physicochemical properties, bioactivity scores and toxicological parameters of the selected compounds were predicted using various computational tools, such as molinspiration, SwissADME, Osiris properties explorer and pKCSM. Furthermore, docking studies were performed against target proteins with PDB IDs– 3V81, 2ZD1, 4JO2 and 3OXX using AutoDock 1.5.7. Among the selected compounds (**1-15**), eightcompounds obeyed Lipinski's rule of five and are expected to show good oral activity and bioactivity. Toxicity variables, such as mutagenicity,tumorigenic effects, etc of a few compounds were identified through the Osiris properties explorer. The application of molecular docking technique has facilitated the exploration of the binding mechanisms between a few drugs and their targets. These computational tools investigated in the present studies provided insights, which will be helpful for future designing novel of antiviral drugs.

Keywords: Computational tools, physicochemical properties, bioactivity, toxicity, docking.

I. INTRODUCTION

Drug discovery and development is an intense, lengthy and an interdisciplinary venture. Conventional drug discovery refers to the traditional approach of identifying and developing new pharmaceutical compounds through a series of experimental and empirical processes.[1] The advancements in computational tools and technologies have significantly impacted drug discovery and development processes in recent times.[2] The **figure 1** depicts various stages of traditional drug discovery and the relevant computer-aided drug discovery tools used to reduce the time taken in traditional drug discovery.

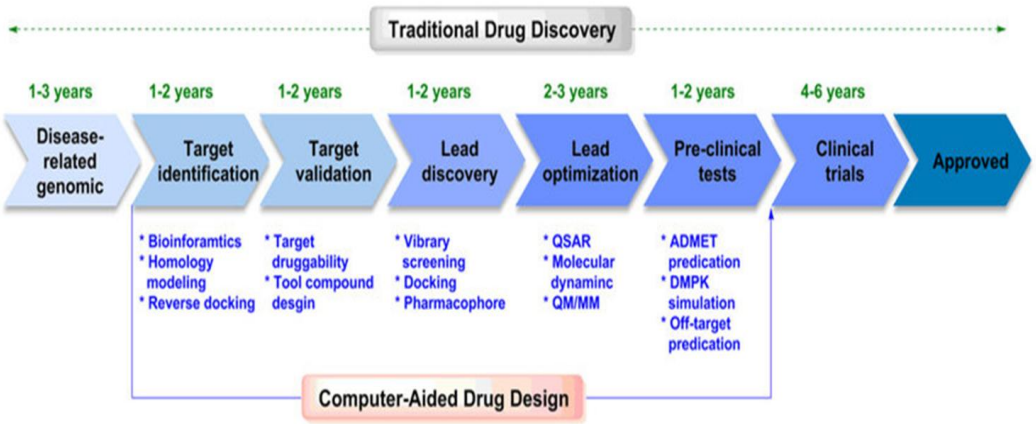

Figure 1. Stages of traditional drug discovery and computer-aided drug design tools

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There are many factors responsible for the failure of drugs, such as lack of effectiveness, side effects, poor pharmacokinetics, and marketable reasons.[3] A trend towards the use of in-silico chemistry and molecular modeling for computer-aided drug design has gained significant momentum in recent times. Drug likeness is defined as a complex balance of various molecular properties and structural features which determine whether a particular molecule is similar to the known drugs. These properties include, hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility. There are various rules such as Lipinski Rule of Five (RO5) describing the molecular properties that are important for pharmacokinetics (absorption, distribution, metabolism and excretion) of the drugs.[4,5]The advantage of these properties is that they can be estimated from the molecular structure before the drug is even synthesized and tested.

The intermolecular interactions in a protein-drug complex are important and require difficult modeling exercises. Docking simulations predict the binding orientation of drug candidates to their protein targets.[6]Usually, the receptor is kept rigid or partially rigid while the conformation of ligand molecules is allowed to change. Overall, computational tools have revolutionized research, analysis, and problem-solving in numerous disciplines. They enhance efficiency, provide valuable insights, and empower researchers to tackle complex problems that would be otherwise challenging or time-consuming to solve using traditional methods.

A wide range of antivirals have been used effectively on a large scale to treat chronic virus infections like HIV and hepatitis C virus, their use to treat acute viral infections has been limited until now by a lack of effective antiviral therapies and a small window of opportunity to apply treatment and improve patient outcomes. But since from the emergence of SARS-CoV-2, most of the scientific research is oriented to identify the molecular features that can effectively address various stages of virus life cycle.[7-11]

Prompted by above findings,a few USFDA approved antiviral drugs were selected and their in silico properties were determined by various computational tools to predict physicochemical properties, bioactivity, in silico binding affinity and toxicity profiles in the present investigation.

II. MATERIALS AND METHODS

Selection of compounds

US FDA approved antiviral agents (**1-15**) of various therapeutic categories were selected for the present investigation. The details of the same were provided in table 1 and Figure 1.

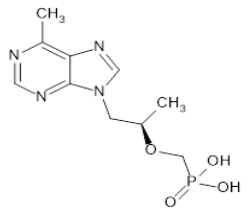
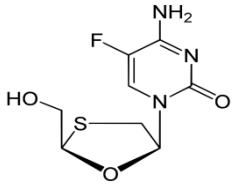
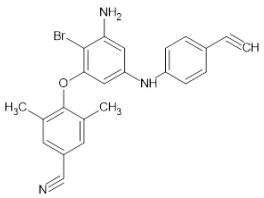
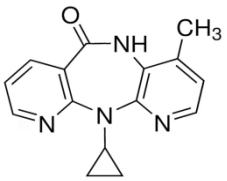
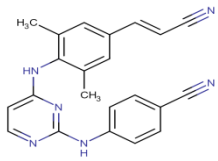
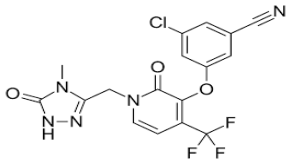
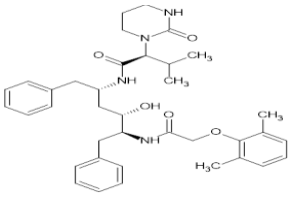
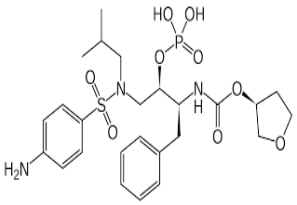
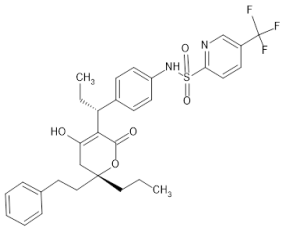
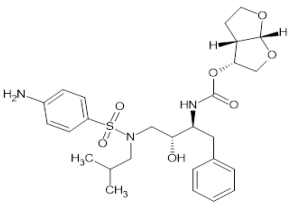
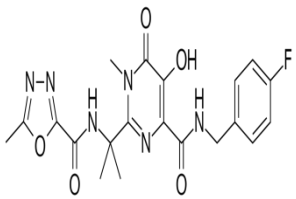
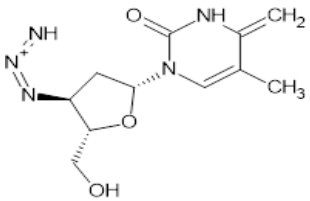
Table 1. Details of selected compounds

S. No.	Drug Name	Therapeutic category	Molecular Formula	Year of FDA Approval
1	Tenofovir	NRTIS	C9H14N5O4P	2001
2	Emtricitabine	NRTIS	C8H10FN3O3S	2003
3	Etravirine	NNRTIS	C20H15BrN6O	2008
4	Nevirapine	NNRTIS	C15H14N4O	2011
5	Rilpivirine	NNRTIS	C22H18N6	2011
6	Doravirine	NNRTIS	C17H11ClF3N5O3	2018
7	Lopinavir	PI	C37H48N4O5	2000
8	Fosamprenavir	PI	C25H36N3O9PS	2020
9	Tipranavir	PI	C31H33F3N2O5S	2005

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1859-1869 www.ijprajournal.com ISSN: 2249-7781

10	Darunavir	PI	C27H37N3O7S	2006
11	Atazanavir	PI	C38H52N6O7	2003
12	Trizivir (zidovudine)	NRTIS	C10H13N5O4	2000
13	Raltegravir	INSTI	C20H21FN6O5	2007
14	Dolutegravir	INSTI	C20H19F2N3O5	2013
15	Elvitegravir	INSTI	C23H23ClFNO5	2014

NRTIS: Nucleotide Reverse Transcriptase Inhibitors; NNRTIS: Non-Nucleotide Reverse Transcriptase Inhibitors; PI: Protease Inhibitors; INSTI: Integrase Strand Transfer Inhibitors.

 1. Tenofovir	 2. Emtricitabine	 3. Etravirine
 4. Nevirapine	 5. Rilpivirine	 6. Doravirine
 7. Lopinavir	 8. Fosamprenavir	 9. Tipranavir
 10.Darunavir	 11.Atazanavir	 12.Trizivir (zidovudine)

International Journal of Pharmaceutical Research and Applications
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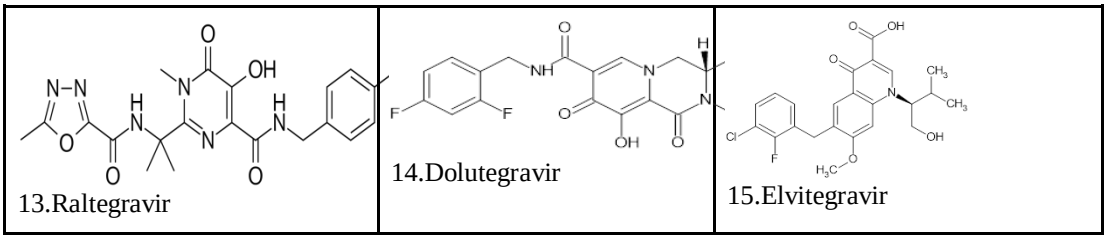

Figure 2. Chemical structures of selected compounds

Prediction of physicochemical properties

Physicochemical properties of the selected antiviral drugs (1-15) were determined by online tools, such as Molinspiration web JME editor[12, 13] and SwissADME.[14] Properties like molecular weight (MW), log P, hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), molar volume (MV) were computed by using Molinspiration tool, while bioavailability and synthetic accessibility scores were determined using SwissADME.

Prediction of bioactivity studies

Bioactivity is predicted by molinspiration, is a measure of the ability of the drug molecule to interact with different receptors, such as GPCR ligands, Kinase inhibitors, Protease inhibitors, Ion channel modulators, or to interact with enzymes and nuclear receptors. Larger the bioactivity score, higher is the probability that the proposed molecules will be active.[15]

Prediction of toxicity

Toxicity prediction of the selected drugs was attempted by using OSIRIS property explorer and pkCSM tools.[16, 17]Toxicity parameters, such as mutagenicity, irritancy, tumorgenicity and reproductivity of the selected antiviral drugs were predicted using OSIRIS property explorer software.This tool is not only useful for the prediction of toxicity, but also for the determination of pharmacokinetic parameters, such as cLogP, solubility, molecular weight, drug-likeness.The predicted results are obtained with color coding.

pkCSM is a machine learning platform which is useful for ADMT predictions. Parameters like maximum recommended tolerated dose (MRTD), lethal dosage (LD_{50}), hepatotoxicity, skin sensitization andT. Pyriformis toxicity of the compounds 1-15 were predicted using pkCSM tool.

In silico molecular docking studies

Docking simulations of the selected antiviral agents (1-15) was performed by using Autodock 1.5.7.[18]Several target proteins were explored initially in Protein data bank. Based on the resolution and year of release a few proteins were considered for docking studies. The details were given in Table 2.Molecular docking involves four steps:

- **Protein preparation:**The X-ray crystal structure of the selected has been downloaded from the RCSB protein data bank. The protein structure was modified by removing water molecules, polar hydrogens were added and Kollman charges were added. The processed protein was then saved as *.pdbqt file.
- **Ligand Preparation**:All the ligands were drawn in chemsketch tool and then it was saved as*.mol file and further it was converted into *.pdb by using Open Babel GUI tool and in Autodock to convert into low energy 3D structures and they were was saved as *.pdbqt file
- **Grid generation**:Receptor grid was generated by selecting suitable x, y, z dimensions for the coordinates with spacing factor 1 to fit the entire protein into a grid box. The output is saved as *.gpf file. The grid file was run for each ligand and the ligand-embedded grid was saved *.dlg file.
- **Docking simulations and analysis**:Docking is performed by using Genetic Algorithm (GA) and the autodock1.5.7 and ligand.*dpf files were used as input. The resulting .dlg file was selected to analyze the output conformations for each ligand. Finally, the confirmation with the least energy (bioactive conformer) was considered and the corresponding conformer-protein complex was visualized to determine the possible ligand-protein interactions.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1859-1869 www.ijprajournal.com ISSN: 2249-7781

Table 2. Details of target proteins selected for the studies

S. No.	Therapeutic category	PDB_ID	Resolution	Year of release
1	NRTIS	**3V81**	2.85Å	2012
2	NNRTIS	2ZD1	1.8 Å	2007
3	PI	4JO2	2.50 Å	2013
4	INSTI	3OXX	2.50 Å	2013

III. RESULTS AND DISCUSSION

For the selected 15 antiviral drugs physicochemical properties, bioactivity scores, toxicity parameters and were predicted using different in silico techniques. The physicochemical properties determined by using molinspiration and SwissADME tools were provided in **Table 3**.Eight out of the fifteen compounds were found to obey Lipinski Rule of Five (RO5) as per the results displayed in **Table 3**. As per RO5, Atazanavir, Tipranavir, Fosamprenavir and lopinavir have showed more number of violations (high MW, Log P & HBA), indicating their poor oral absorption. Remaining drugs were showing either zero or one violation, indicating their good oral absorption as per the predictions.Drug-likeness score was found maximum in case of Tenofovir, Lopinavir and Trizivir among the evaluated compounds.A positive drug score indicates the predominance of the pharmacophoric moieties in the molecule. All the compounds showed a positive value in the drug score calculation and were in the range of 0.24-0.93.Greater drug score was observed for the drugs Emtricitabine, Nevirapine, Raltegravir and Dolutegravir.

Table 3. Physicochemical properties of selected antiviral drugs (1-15)

Drugs	Log P	TPSA	MW	HBA	HBD	violation	nrotbe	volume	Drug likeness	Drug score
Tenofovir	-0.62	136.39	287.22	9	4	0	5	232.58	7.64	0.24
Emtricitabine	-0.67	90.38	247.25	6	3	0	2	192.01	1.29	0.87
Etravirine	5.03	120.65	435.29	7	3	0	4	335.95	-1.00	0.63
Nevirapine	1.39	63.58	266.30	5	1	0	1	236.62	3.02	0.93
Rilpivirine	5.46	97.42	366.43	6	2	1	5	337.61	-7.88	0.36
Doravirine	2.08	105.72	425.75	8	1	0	5	320.43	-10.38	0.33
Lopinavir	5.69	119.99	628.81	9	4	2	15	607.96	7.64	0.24
Fosamprenavir	3.47	177.73	585.62	12	5	2	14	504.08	-32.37	0.32
Tipranavir	8.10	105.59	602.67	7	2	2	12	517.66	-6.92	0.20
Darunavir	4.32	140.43	547.67	10	4	1	12	490.57	-12.81	0.33

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1859-1869 www.ijprajournal.com ISSN: 2249-7781

Atazanavir	7.97	171.22	704.87	13	5	3	18	670.23	-15.63	0.25
Trizivir (zidovudine)	-0.10	134.08	267.25	9	2	0	3	224.06	7.64	0.24
Raltegravir	-0.81	152.25	444.42	11	3	1	6	375.58	7.28	0.83
Dolutegravir	0.92	100.87	419.38	8	2	0	3	345.56	5.64	0.86
Elvitegravir	3.58	88.77	447.89	6	2	0	7	383.2	1.08	0.32

The bioactivity data determined by molinspiration and the bioavailability score and synthetic accessibility score detrmined from SwissADME tools were given in **Table 4**.The GPCR ligand activity, Ion channel modulation and kinase inhibitor activity of Tenofovir was found to be significant among the tested antiviral drugs.Highest Protease inhibition was observed for Fosamprenavir and Darunavir. Presence of sulfonamide group may be attributed to the protease inhibitor activity of these drugs. The enzyme inhibitory activity of Tenofovir was evidenced through in silico predictions as its shown highest value (1.54) among all. The poor bioavailability of Atazanavir is observed in the predictions, which may be due to its high molecular weight and Log P values (**Table 3 and 4**).The significance of synthetic accessibility score is to determine the ease of synthesis of compounds. The scale ranges from 1-10. The value towards 1 denotes that the compound can be easily synthesized and the value approaching to 10 denotes that its difficulty in the synthesis. The predicted synthetic accessibility data are in the range of 2.30-6.24. The ease of synthesis of Nevirapine was evidenced in the predictions, as its score showing the least value (2.30) among all.

Table 4. Bioactivity and bioavailability and synthetic accessibility datapredicted for selected antiviral drugs (**1-15**)

Drugs	**GPCR Ligand**	**Ion channel modulator**	**Kinase inhibitor**	**Nuclear receptor ligand**	**Protease inhibitor**	**Enzyme inhibitor**	**Bioavailability Score**	**Synthetic accessibility**
Tenofovir	**0.60**	**0.73**	**0.80**	-0.90	0.29	**1.54**	0.56	3.39
Emtricitabine	-0.02	-0.38	-0.13	-1.42	-0.24	**1.32**	0.55	3.67
Etravirine	-0.01	-0.08	**0.49**	-0.31	0.00	0.22	0.55	3.29
Nevirapine	-0.12	-0.41	0.08	-0.72	-0.52	**0.58**	0.55	2.30
Rilpivirine	0.06	-0.13	**0.72**	-0.27	-0.17	0.20	0.55	3.29
Doravirin	0.03	-0.38	0.14	0.07	-0.10	-0.01	0.55	3.28

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1859-1869 www.ijprajournal.com ISSN: 2249-7781

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Lopinavir	0.04	-0.78	-0.55	-0.66	0.42	-0.37	0.55	5.67
Fosamprenavir	**0.54**	0.02	0.09	-0.16	**1.07**	0.064	**0.11**	5.43
Tipranavir	-0.02	-0.45	-0.62	-0.16	0.22	-0.13	0.56	5.29
Darunavir	**0.35**	-0.21	-0.24	-0.26	**1.15**	0.31	0.55	5.67
Atazanavir	-0.41	-1.66	-1.17	-1.39	0.26	-0.70	**0.17**	6.24
Trizivir (zidovudine)	**0.41**	-0.08	-0.15	-0.79	-0.02	**1.17**	0.55	3.93
Raltegravir	-0.03	-0.43	0.00	-0.39	0.11	0.13	0..55	3.49
Dolutegravir	0.05	-0.20	-0.04	-0.02	0.04	0.07	0.55	4.16
Elvitegravir	0.08	-0.25	-0.16	0.07	0.18	0.38	0.56	3.51

The toxicity predictions determined for the selected drugs using OSIRIS property explorer and pKCSM tools were provided in **Table 5**. The toxicity scores predicted by Osiris proeperty explorer were color-coded, where green indicates probable activity. Properties with high risks of undesired/toxic effects such as mutagenicity, tumorogenic, etc are shown in red, the compounds with mild toxic effects are indicated ad orange, while the drugs with low probability of such effects are indicated as green color.

Table 5. Toxicity data predictions using Osiris property explorer and pKCSM tools

Drugs	**Mutagenic**	**Tumorigenic**	**Irritant**	**Reproductive effect**	**LD_{50}**	**Hepatotoxicity**	**Skin sensitivity**	**T.Pyriformis toxicity**
Tenofovir	Green	Green	**Red**	Green	2.176	Yes	No	0.285
Emtricitabine	Green	Green	Green	Green	1.761	Yes	No	0.203
Etravirine	Green	Green	Green	Green	2.873	Yes	No	0.293
Nevirapine	Green	Green	Green	Green	2.715	Yes	No	0.332
Rilpivirine	Green	Green	Green	Green	2.62	Yes	No	0.366
Doravirine	Green	Orange	Green	Green	2.689	Yes	No	0.303

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1859-1869 www.ijprajournal.com ISSN: 2249-7781

Lopinavir	Green	Green	**Red**	Green	2.482	**No**	No	0.285
Fosamprenavir	Green	Green	Green	Green	2.204	Yes	No	0.285
Tipranavir	Green	Green	Green	Green	2.367	Yes	No	0.286
Darunavir	Green	Green	Green	Green	2.107	Yes	No	0.289
Atazanavir	Green	Green	Green	Green	2.665	Yes	No	0.285
Trizivir (zidovudine)	Green	Green	**Red**	Green	2.161	Yes	No	0.23
Raltegravir	Green	Green	Green	Green	1.702	Yes	No	0.286
Dolutegravir	Green	Green	Green	Green	1.921	Yes	No	0.301
Elvitegravir	**Red**	**Red**	Green	Green	2.377	Yes	No	0.285

The mutagenic and the tumerogenic effects of the drugs (1-15) were found to be almost negligible, except for Elvitegravir. The irritant effect of the drugs Tenofovir, Lopinavir and Trizivir were found to be significant among all. All the drugs have no predicted reproductive effects and they are not sensitive toward skin but all are predicted to have hepatotoxicity with the exception for Lopinavir. The LD_{50} values were found to be in the range of 1.702-2.873. The T. Pyriformis toxicity score of all the selected compouds was found to be >-0.5, indicating their high level of toxicity against that protozoa.

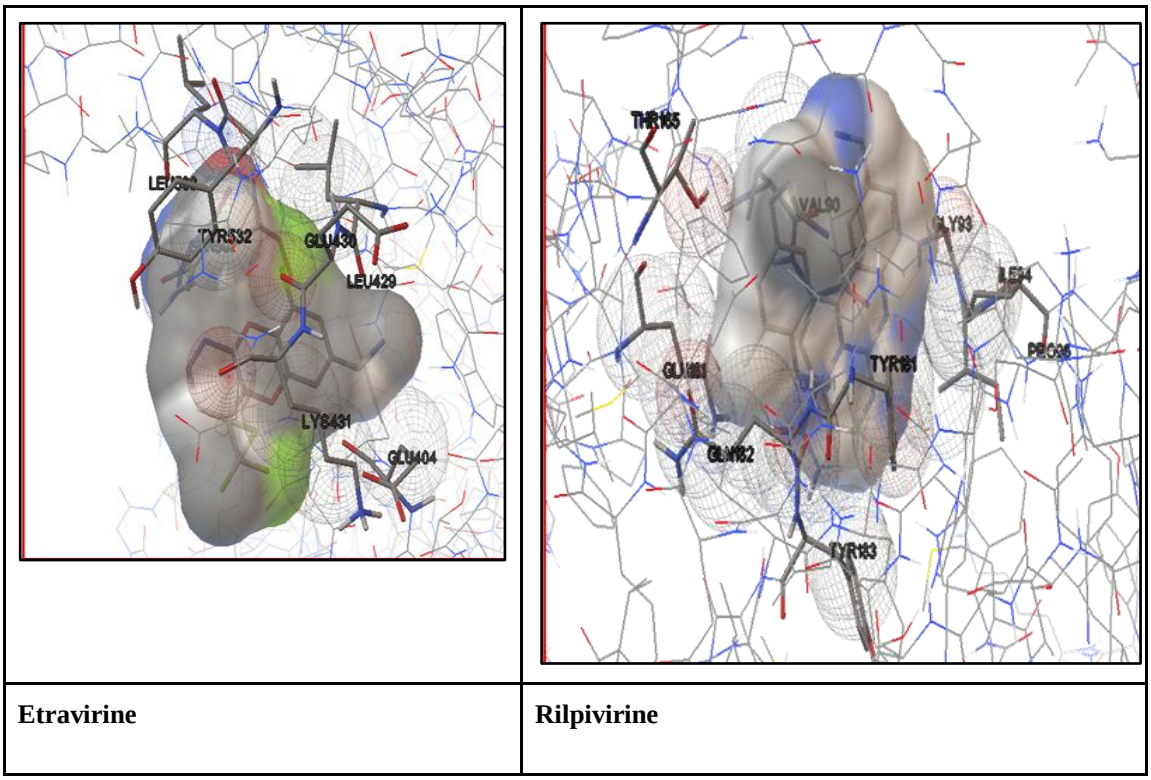
In silico molecular docking studies of the selected antiviral drugs was performed by using freely available tool AutoDock 1.5.7.The target proteins were selected form PDB, depending on the mode of action of specific antiviral drugs. The target protein for each antiviral drug and binding energies of the resulting protein-drug complex were provided in **Table 6**.As per the docking poses represented in **Figure 2**, Both the NNRTI drugs (Etravirine and Rilpivirine) binding with amino acid residues Glutamic acid 430 on the active site of 2ZD1.Among the drugs docked against 2ZD1, Etravirine has shown highest binding energy (-7.33 Kcal/mol). Protease inhibitor, Darunavir interaction with its target (4JO2) resulted in high docking score (-7.25 Kcal/mol), among the tested PIs.

Table 6. Binding energies of selected drugs usingAutodock1.5.7

Compound code	**Drugs**	**Target protein PDB-ID**	**Binding Energy (Kcal/mol)**
01	Tenofovir	NRTIS - **3V81**	-5.78
02	Emtricitabine		-6.09
03	Etravirine	NNRTIS - 2ZD1	-7.33
04	Nevirapine		-6.90
05	Rilpivirine		-6.77
06	Doravirine		-6.48

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1859-1869 www.ijprajournal.com ISSN: 2249-7781

07	Lopinavir	PI - 4JO2	-5.74
08	Fosamprenavir		-6.25
09	Tipranavir		-7.20
10	Darunavir		-7.25
11	Atazanavir		-4.64
12	Trizivir (zidovudine)	NRTIS - **3V81**	-4.58
13	Raltegravir	INSTI - 3OXX	-6.65
14	Dolutegravir		-5.59
15	Elvitegravir		-5.80



Etravirine | **Rilpivirine**

Figure 2. Molecular interactions of NNRTI drugs on the active site of 2ZD1.

IV. CONCLUSION

Selected US FDA approved antiviral agents (**1-15**) were evaluated for various pharmacokinetic, biological and toxicological activity predictions using freely available online tools.Eight antiviral drugs, namely Tenofovir, Emtricitabine, Etravirine, Nevirapine, Doravirine, Trizivir, Dolutegravir and Elvitegravir were found to obey RO5 indicating their better oral absorption. Atazanavir has poor oral absorption as per RO5 (no. violations = 3). The same is evidenced in bioactivity prediction. Its protease inhibitor activity is also evidenced in bioactivity predictions. As per RO5 predictions, Fosamprenavir also showed violations (2). But being a prodrug, it rapidly converts in to active form, Amprenavir.Highest

Protease inhibition was observed for Fosamprenavir and Darunavir. Presence of sulfonamide group may be attributed to the protease inhibitor activity of these drugs.The probability of protease inhibition of darunavir was also indicated through docking studies against 4JO2. Both the NNRTI drugs (Etravirine & Rilpivirine) binds with the similar amino acid residues on the active site of 2ZD1, indicating the common mode of binding of these drugs on the target protein. The knowledge gained in understanding of pharmacophoric requirements through above studies is useful to design novel antiviral agents in the future.

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