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In-silico molecular docking and ADMET studies of new thiazolopyrimidine derivatives with anti-HIV-1 non-nucleoside reverse transcriptase activity

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ABSTRACT: In this study, the interaction between human immunodeficiency virus reverse transcriptase and Thiazolopyrimidine containing various substituents was studied by molecular docking simulation followed by ADMET prediction and molecular docking was accomplished with Auto Dock, PyRx. Swiss-adme and Protox II servers were used to predict the pharmacokinetics and absorption, distribution, metabolism, excretion and toxicity properties of all compounds. As a result, molecular docking analysis revealed that there are extensive interactions between the thiazolopyrimidine derivatives and residues in the active site of human immunodeficiency virus-1 reverse transcriptase. The formation of hydrogen bonds between thiazolopyrimidine derivatives and the residues Lys101 and Glu138 play important roles in inhibiting the activity of human immunodeficiency virus. All compounds respect the conditions mentioned in Lipinski's rule and have acceptable absorption, distribution, metabolism, and excretion and toxicity properties. The thiazolopyrimidine derivatives substantially improved the potency against wild-type human immunodeficiency virus-1 and several mutant strains, and the 2nd position is the most preferred position to improve antiviral activity. This information might be helpful for further thiazolopyrimidine optimizations.

KEYWORDS: ADMET, Thiazolopyrimidine, Molecular Docking, Pharmacokinetics, Autodock, PyRx.

I. INTRODUCTION

Human Immunodeficiency Virus type 1 (HIV-1) is the primary cause of Acquired Immunodeficiency Syndrome (AIDS), which is still a serious public health issue on a global scale. [1] HIV-1 Reverse Transcriptase (RT) converts the single-stranded Ribonucleic Acid (RNA) genome into a double-stranded Deoxyribonucleic Acid (DNA) copy, which is necessary for HIV-1 replication and has been identified as a promising therapeutic target for the development of anti-HIV drugs. [2] Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) can be disrupted by NNRTIs, which can attach to a hydrophobic allosteric binding pocket (NNRTI Binding Pocket, NNIBP) that is situated at position 10 from the RT polymerase active site. [3] Components of Highly Active Antiretroviral Treatment (HAART) have a special antiviral potency. [4]

Despite having a number of benefits, only four NNRTIs- Rilpivirine (RPV), Nevirapine (NVP), Delavirdine (DLV), Efavirenz (EFV) and Etravirine (ETV), have received clinical use approval from the Food and Drug Administration (FDA). [5,7] First-generation NNRTIs include NVP, DLV and EFV, but their therapeutic efficacy has been dramatically understated due to the rapid emergence of HIV-1 drug resistant variants such as Tyr181, Lys103 and Tyr188 single mutants, as well as Lys103/Tyr181 double mutant (RES056 Lys103+Tyr181). [6] In order to combat the AIDS epidemic, the United States (US) FDA approved the next-generation HIV-1 NNRTIs Rilpivirine (RPV, **fig. 1**) in 2011. [16]

The thiazolopyrimidine compounds are important in the non-nucleoside reverse transcriptase inhibitors, because it has a strong inhibitory activity and small toxic side effects on single mutation and double mutation. Rilpivirine is pyrimidine containing NNRTIs with high activity against Wild-Type (WT) and mutant virus strains including Lys103. [17]

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Fig. 1: Chemical structure of NNRTI drug: Rilpivirine (RPV)

However, the resistant variants Glu138 and Lys103/ Tyr181, can still significantly decrease the sensitivity of HIV-1 to RPV. [8] Therefore, there is a need of developing novel NNRTIs with enhanced therapeutic value and different resistance mutation profiles to successfully employ this class of drugs in HAART. [9] A series of new NNRTIs has been found and synthesized in the ongoing study of NNRTIs in the last decade. Thiazolopyrimidine is one of them and a design feature for these compounds is the innate flexibility between aromatic rings, allowing the compound to adopt multiple conformations and is one explanation for the potent activity against many resistant virus strains (**fig. 2**). So it has a promising prospect of development and application. [17]

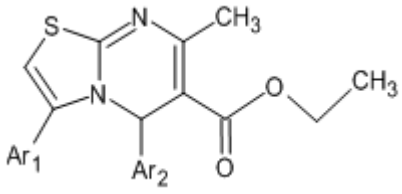

Fig. 2: The general structure of TZPs

In this study, we have taken 10 thiazolopyrimidine that displayed the most potent anti-HIV-1 activity, with excellent selectivity for infected over uninfected cells (**Table no.: 1**). Thiazolopyrimidine derivatives studied in-silico for their potential anti-HIV activity along with their physicochemical and Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties and the discussions were also investigated together with the comparative docking analysis. [10]

Table no. 1: Thiazolopyrimidine Derivatives

Derivatives	R_1	R_2
D1	4-Hydroxy	4-Methoxy
D2	2-Bromo	P-Dimethyl Amino
D3	4-Hydroxy	2-Hydroxy
D4	4-Hydroxy	2-Chloro
D5	4-Hydroxy	4-Nitro
D6	4-Nitro	4-Hydroxy
D7	4-Nitro	4-Chloro
D8	4-Nitro	2- Nitro
D9	4-Nitro	3-Nitro
D10	4-Nitro	4-Methoxy

The SwissADME and admetSAR were used to analyse the pharmacokinetic properties of TZPs. The Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) was used to obtain protein crystal structures based on resolution and R factors. [10, 11]

The compounds chosen from structure-based virtual screening were evaluated for drug-likeness and Lipinski's "rule of five" parameters, which included molecular weight, number of Hydrogen (H)-bond donors, number of H-bond acceptors and partition coefficient. A drug or compound that is taken orally should have a molecular mass of 500 Daltons (Da), calculated octanol/water partition coefficient (CLogP) < 5, number of hydrogen-bond donors < 5 and number of hydrogen-bond acceptors < 10. These properties are then typically used to construct predictive ADME models and form the basis for what has been called property-based design. To a certain extent, similar molecules can be expected to have similar ADME properties. While Veber et al. suggested that a molecule or medicine should have a Topological Polar Surface Area (TPSA) value of

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1402 and a number of rotatable bonds of at least 10. All of these guidelines must be followed in order for a medicine or chemical to be deemed to have good oral bioavailability. Using the online SwissADME calculator, all of these physicochemical characteristics and drug-likeness factors were determined. [10]

II. MATERIALS AND METHODS

2.1 Platform for molecular docking:

The computational docking assessment of 10 thiazolopyrimidine derivatives for the Non-nucleoside reverse transcriptase activity was performed using the AutoDock Vina software. [12]

2.2 Preparation of proteins and grids

In silico analysis of 10 thiazolopyrimidine derivatives were performed using a 1.80 Å crystal structure of 2ZD1 from the HIV-1 reverse transcriptase in complex with TMC278 (Rilpivirine), a non-nucleoside RT inhibitor. (PDB ID: 2ZD1, with a resolution < 2 Å, R-value free < 0.25 and R-value work < 0.25) which was retrieved from the PDB. The protein preparation parameters of AutoDock were then used to prepare the whole structure by deleting water molecules, adding hydrogen, and assigning partial charges using Kollman and Gasteiger, and the binding sites were identified after deleting the ligand. [15]

2.3 Ligand preparations

For the preparation of ligand, **12** TZPs derivatives structure was drawn with the help of ChemSketch software and geometric optimization was carried out with the help of Avogadro. [19]

2.4 Protein ligand docking and visualization

AutoDock Vina was used in all the docking experiments, using the optimized model as the docking target. Computational docking is executed to generate a population of promising orientations and conformations of the ligand within the binding site. The grid centre for docking was set at X = 50.481, Y = – 27.510, and Z = 37.039, with the grid box set to 40 Å × 40 Å × 40 Å. Derivatives were individually evaluated in the molecular docking. [12]

2.5 Physicochemical properties

The compounds chosen from structure-based virtual screening were evaluated for drug-likeness properties. Lipinski's rule and Veber's rule were used to assess the physicochemical properties of all the selected thiazolopyrimidine derivatives and predict their drug-like properties. Using the online SwissADME calculator, all of these physicochemical characteristics and drug-likeness factors were determined. [13]

2.6 ADMET properties

Swiss ADME (http://www.swissadme.ch/) was used to compute the SMILES structures of each compound. **Protox II** was used to predict the carcinogenicity, mutagenicity, irritant, reproductive impacts and ADMET characteristics of 10 compounds that were anticipated to be active. [18]

III. RESULTS AND DISCUSSION

3.1 Physicochemical properties

Lipinski's rule of five and Veber's rules were used to check the drug-likeness.

Table 2: physicochemical properties of Thiazolopyrimidine derivatives

Name	Lipinski's Rule of 5					Veber's rule	
	LogP	Molecular Weight (g/mol)	HBD	HBA	Violations	TPSA	Rotable Bonds
D1	4.12	422.49	0	3	0	123.77	6
D2	3.46	498.43	1	5	0	99.98	5
D3	3.39	408.07	0	3	0	94.19	4
D4	3.45	426.98	0	4	0	81.83	4
D5	3.25	437.46	0	3	0	118.41	3
D6	4.02	437.46	0	3	0	125.67	4
D7	3.59	455.91	0	3	0	100.08	5
D8	4.09	466.46	1	4	0	112.38	6
D9	4.09	466.46	1	4	0	123.41	5
D10	3.82	451.49	0	3	0	108.98	3

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(HBD: Hydrogen bond donors, HBA: Hydrogen bond acceptor, TPSA: Total polar surface area)
Pharmacokinetic studies of TZP's were explained here. Pharmacokinetic properties are an elemental segment of drug development to identify the biological properties of drug candidates. Lipinski's rule of five and Veber's rules were used to check the drug-likeness.

TZPs given in **Table 1** were analysed for their physicochemical properties and the results are optimized in **Table 2**. The ADMET characteristics of the TZPs were studied to understand their pharmacokinetic profile and the results are given in **Table 4**. Out of 10 TZPs listed in **Table 2**, all TZPs are showing no violation of the Lipinski's and Vebrules and hence display Drug-Like Molecular (DLM) nature. The Log P values of TZPs are within the range. Molecular weight, number of H-acceptors and H-bond donors of all TZPs are within the accepted values of less than 500, 10 and 5 respectively (**Table 2**) and all the TZPs are following the criteria of Veber's rules with Total Polar Surface Area (TPSA) values and the count of rotatable bonds within range for oral availability. [10]

3.2 ADMET properties

We also assessed the in silico ADMET properties of two well-known drugs to validate the in silico protocol (ETV and RPV). The findings showed that every substance tested, including ETV and RPV, could pass through the BBB and absorb in the human intestine (**Table 4**). Drugs are metabolized by Cytochrome P450 (CYP450) isozyme, which aids in drug excretion from the body and lessens the impact of the drug. These isozymes also have a significant impact on medication interactions.

3.3 Molecular Docking studies

Molecular docking was carried out using the AutoDock program in order to explore the binding manner of TZPs in the NNIBP of WT HIV-1 RT to determine the kinds of interactions and the binding affinities of the investigated compounds in the investigated enzyme, molecular docking was used. 10 different TZPs compounds have been evaluated for their affinity against the HIV RT protease. The results are presented in **Table 3**. The lowest binding free energy between HIV RT and TZPs was calculated on the basis of the molecular docking simulation and compared with the standard.

Table 3: Molecular docking studies

Receptor (PDB ID)	**Derivatives**	**Binding Affinity**
2ZD1	D1	-7.8
	D2	-7.5
	D3	**-8.7**
	D4	**-8.5**
	D5	**-8.4**
	D6	-8.1
	D7	-8.0
	D8	-7.7
	D9	-7.6
	D10	-7.5
	Standard (Rilpivirine)	**-8.4**

The compounds with lower binding energy can have a higher affinity towards target proteins. These conformations are the configuration with the lowest binding auto kinetic energy after compound molecules were docked with HIV-1 RT and binding energy of standard is -8.4 kcal/mol. Binding interaction of D3, D4, and D5 is given in Figure 3.

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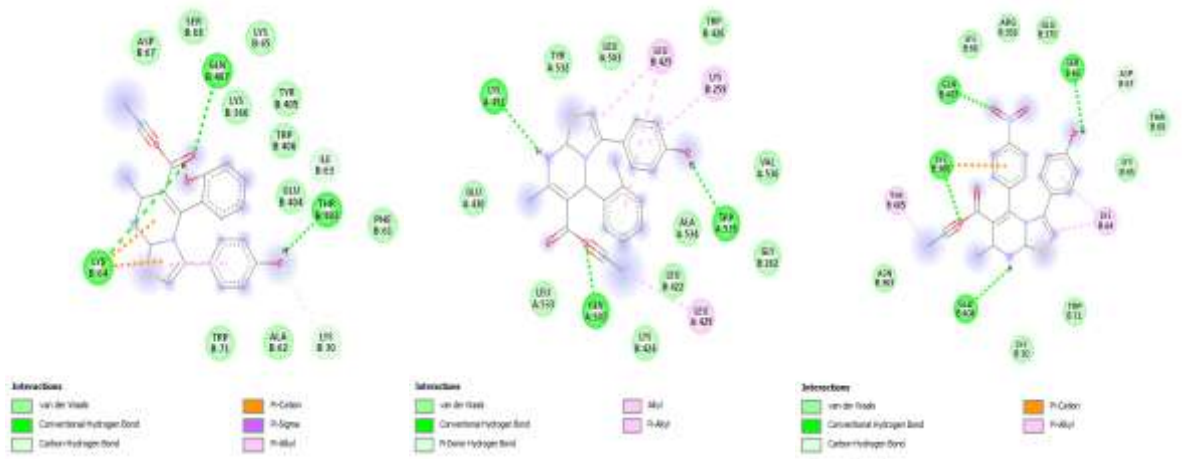

Fig. 3: Bindin (A) on of 2 ZD1 with A) D3 (B) ling affinity -8.7 B) D4 (C) ing affinity -8.5 C) D5 with binding affinity -8.4

So, there are three derivatives which having higher binding affinity compared to standard i.e., D3, D4, D5 with binding affinity -8.7, -8.5, -8.4 respectively.

Table 4: ADMET characteristics of the TZPs

Name	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Rilpivirine
BBB	0.732	0.7123	**0.8521**	**0.8427**	**0.8313**	0.7636	0.6523	0.7098	0.7098	0.7640	**0.8571**
HIA	0.9565	0.8323	**0.9925**	**0.9905**	**0.9865**	0.9085	0.8996	0.9560	0.8879	0.9504	**0.9929**
Renal OCT	NI	NI	**NI**	**NI**	**NI**	NI	NI	NI	NI	NI	**NI**
CYP450 2C9 substrate	NS	NS	**NS**	**NS**	**NS**	NS	NS	NS	NS	NS	**NS**
CYP450 2D6 substrate	NS	NS	**NS**	**NS**	**NS**	NS	NS	NS	NS	NS	**NS**
CYP450 1A2 inhibitor	NI	NI	**I**	**I**	**I**	I	I	I	I	NI	**NI**
AMES toxicity	NT	T	**NT**	**NT**	**NT**	T	T	T	T	NT	**NT**
Carcinogenicity	NC	NC	**NC**	**NC**	**NC**	NC	NC	NC	NC	NC	**NC**

(Note: Blood-Brain Barrier (BBB): Don't cross BBB (–); cross BBB (+); Human Intestinal Absorption (HIA): Not absorbed (–); absorbed (+), CYP450: S=Substrate for enzyme; NS=Not a substrate for enzyme; I=Enzyme inhibitor; NI=Not enzyme inhibitor; NT: Nontoxic; T: Toxic and NC: No carcinogenic)

The gastrointestinal absorption of the thiazolopyrimidines has shown high absorption rate. The distribution of drug candidates considers the BBB permeability. The metabolism and total clearance of the thiazolopyrimidines were analysed. The thiazolopyrimidines 3 derivatives are there which showed Ames non-toxicity with CYP450 1A2 inhibitory activity. In a collective sense, the ADMET profile of the Thiazolopyrimidines is satisfactory and hence suitable for in silico studies with HIV proteins.

IV. CONCLUSION

In this study, the interaction between HIV RT and Thiazolopyrimidines molecules was stimulated by molecular docking, show that the binding mechanism between Thiazolopyrimidine derivatives and RT was expounded. This work might provide useful information for guiding the rational design of potential HIV-1 NNRTI Thiazolopyrimidines. Thiazolopyrimidines superior pharmacological characteristics and distinctive molecular binding method will keep medicinal chemists motivated to discover additional effective HIV-1 NNRTIs. We evaluated a library of 10 thiazolopyrimidine derivatives and revealed that D3, D4, D5 bind the target efficiently and may have value as potential inhibitors. Thus, we conclude that these thiazolopyrimidines can be

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used as potential antiviral candidates and suggest that further in vitro or in vivo experiments may provide better insight for preventing and treating HIV.

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