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Molecular Docking and *In Silico* ADME Evaluation of Indolizine Analogues as Potential Anti - HIV Agents

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ABSTRACT

The Human Immunodeficiency Virus (HIV), the causative agent of Acquired Immunodeficiency Syndrome (AIDS), has several key enzymes, including HIV-1 Reverse Transcriptase (RT), which are important targets for the development of antiviral drugs. Since HIV is a retrovirus that utilizes RT for replication, the development of therapies targeted at RT is essential for treating HIV-1 infections. The goal of this project was to computationally design and evaluate 100 different analogues of indolizine for potential inhibitory activity against HIV-1 RT. The compounds were designed using ACD/ChemSketch, and their potential drug-like properties were evaluated using Molinspiration. Four (IN1, IN2, IN32 and IN33) of the compounds adhered to Lipinski's Rule of Five. The predictions made via PASS Online indicated that the four designed compounds will have the ability to inhibit RNA directed DNA polymerases. The biological potential of all designed analogues was evaluated via molecular docking studies with AutoDock 4 using Delavirdine as a reference compound against the wild-type (PDB ID: 1KLM) and mutant (PDB ID: 1JLB) forms of HIV-1 RT enzyme. Of all the evaluated compounds, IN1 had a significantly greater binding affinity for both wild-type and mutant HIV-1 RT, while IN33 interacted well with wild-type HIV-1 RT. SwissADME and ADMETlab v3.0 were used to perform ADMET analysis on all the compounds to predict acceptable drug-like properties for all compounds. The results indicate that indolizine derivatives, particularly IN1, are promising lead compounds for drug development.

Keywords: AIDS, HIV, Molecular Docking, *In silico* Studies

INTRODUCTION

Acquired Immuno Deficiency Syndrome (AIDS) is a condition manifested by a group of diseases caused by Human Immuno Deficiency Virus (HIV). HIV targets the body's white blood cells leads to weakening the immune system. HIV belongs to a class of virus known as Retrovirus. They store their genetic information as ribonucleic acid (RNA). Before the replication phase, they undergo reverse transcription (RNA converted to DNA) in the presence of an enzyme HIV Reverse Transcriptase (RT). Mechanism involved in the HIV in the host cells are, they incorporate their genetic material into the host cells. In this way, they conceal their presence from the immune system and adapting to new conditions. HIV can be categorized into, HIV-1 and HIV-2. HIV-1 is common and more virulent, responsible for the global HIV pandemic, higher transmission rate and faster disease progression whereas HIV-2 is less common and less virulent, Slow disease progression. The HIV lifecycle begins with an interaction between the virion glycoprotein (Gp120) situated on the outer membrane and CD4 receptor on the host cell surface results in the conformational changes in the receptor. Gp120 interacts with chemokine co-receptor CXCR4 or CCR5 leads to further conformational changes, fuses viral envelope and cell membrane and the virion decapsulated releasing the viral RNA into the host cell's cytoplasm. Later it undergoes reverse transcription which is catalyzed by an enzyme RNA dependent DNA polymerase also known as HIV Reverse Transcriptase (RT). After reverse transcription, it is integrated into the host chromosome and replication occurs which leads to the building of long chains of HIV proteins. Viral Assembly of the HIV proteins occur near the cell membrane which leads to budding which involves immature HIV converted into mature HIV in the presence of Protease enzyme. RT is a Viral enzymatic protein found within Retroviruses, including HIV, which enables cellular synthesis of complementary DNA from Viral RNA, ultimately reversing the host organism's standard process of transcription for genetic material. The RT enzyme within HIV is encoded by pol Genes forming heterodimers of the RT enzyme with two distinct subunits (p66/p51). The RT enzyme exerts three known Enzymatic Activities, ultimately forming the final product of Double-Stranded Viral DNA. There is a very high mutation rate associated with Reverse Transcriptase as there is no 'Proofreading' associated with it meaning there is significant diversity among the HIV Virus and the associated Drug-Resistant/Viral Lineages. [5,8,9]

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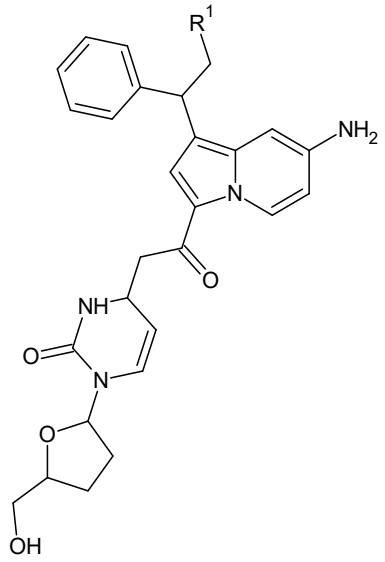
Indolizine is an aromatic organic compound with a molecular formula C8H7N, which is an isomer of Indole but differ in the arrangement of atoms and ring fusion. Although both are isomers of each other, indolizine displays higher aromatic and planarity characteristics compared to indole, due to which its unique biological properties make it very attractive in medicinal chemistry for developing new drugs. However, the high replication rate of HIV leads to RT mutations that may result in drug resistance. Mutations associated with HIV-1 RT that affect both the NRTIs and NNRTIs interaction regions can lead to loss of inhibitor binding affinity.[1]

Our aim of this study is to explore the Anti-HIV potential of Indolizine analogues by computational methods including molecular docking against Wild type protein (PDB ID: 1KLM) and Mutant type protein (PDB ID: 1JLB) to evaluate their capability to overcome drug resistance.

Rational Drug Design and Structure Active Relationship

The fused bicyclic heteroaromatic indolizine is a frequently employed electron-rich C-1 and C-3 position for electrophilic aromatic substitution reactions. Thus, the C-1 and C-3 positions are frequently selected by medicinal chemists to alter chemical structures (e.g., add a new substituent) to enhance the biological activity of an indolizine while maintaining the aromatic structural integrity. Through the addition of substituents at each of these positions, functional groups can be directed (i.e., projected) outward from an indolizine structure without affecting the conjugated core system.[1,2]

Based on the SAR, the present analogue designed by maintaining the core indolizine structure that provides benzoic ring-like conjugation and thus maintains both aromatic stability and biological activity, an indolizine analogue has been developed. When working within the indolizine field, substitutions often occur at electron-rich sites (i.e., C-1 and C-3).In the design of the current indolizine analogue, functional groups have been added in ways that do not interfere with the fused aromatic ring conjugation systems, hence are able to maintain basic three-dimensional structural integrity. To provide additional hydrophobic and π–π stack-like forces of attraction between the receptor-binding pocket and these molecules, phenyl groups were utilized. To attach functional groups providing sites of hydrogen donor (amide) and acceptor (carbonyl), bonds could also facilitate increased strength (greater nip) of ligand–protein interaction. Finally, a polar group side chain was included to accomplish higher levels of solubility and flexibility in binding interactions. For example, with Delavirdine, non-nucleoside reverse transcriptase inhibitors exhibit that the aromatic rings provide hydrophobic attraction in the binding pockets, while amide (or similar) connections provide for hydrogen bonding ability with crucial amino acid moieties. Thus, in another aspect, the present indolizine analogue provides an aromatic core with hydrogen bonding capabilities as well.[1,2,3,4]



CODE	R	CODE	R	CODE	R
IN1	OH	IN36	$C(i\text{-}Pr)_3$	IN71	$COCH_2NH_2$
IN2	CH_3	IN37	Cph_3	IN72	Phe
IN3	CH_2CH_3	IN38	CH_3ph	IN73	Arg
IN4	$CH_2CH_2CH_3$	IN39	COph	IN74	His
IN5	$CH_2CH_2CH_2CH_3$	IN40	CO(i-Pr)	IN75	Pro
IN6	$CH_2CH_2CH_2CH_2CH_3$	IN41	CO(t-Bru)	IN76	Lle
IN7	$CH_2CH_2CH_2CH_2CH_2CH_3$	IN42	$COCH_3$	IN77	Asn

IN8	NH_2	IN43	$CONH_3$	IN78	Ser
IN9	NO_2	IN44	COCl	IN79	Asp
IN10	Ph	IN45	COOH	IN80	Leu
IN11	$PhCH_3$	IN46	$COOCH_3$	IN81	Thr
IN12	$PhCH_2CH_3$	IN47	$COOCH_2CH_3$	IN82	Cys
IN13	$PhCH_2CH_2CH_3$	IN48	COOph	IN83	Lys
IN14	$PhCH_2CH_2CH_2CH_3$	IN49	NCO	IN84	Trp
IN15	$PhCH_2CH_2CH_2CH_2CH_3$	IN50	ONO_2	IN85	Gly
IN16	$PhNH_2$	IN51	NCS	IN86	Met
IN17	$PhNO_2$	IN52	$NHCOCH_3$	IN87	Tyr
IN18	CHO	IN53	SO_2H	IN88	Glu
IN19	CH_2OH	IN54	OPO_2H_2	IN89	Orn
IN20	CH_2CH_2OH	IN55	NO	IN90	Val
IN21	$CH_2CH_2CH_2OH$	IN56	OCN	IN91	t-Butyloxycarbonyl
IN22	$CH_2CH_2CH_2CH_2OH$	IN57	OCHO	IN92	Benzyloxycarbonyl
IN23	$CH_2CH_2CH_2CH_2CH_2OH$	IN58	SO_2NH_2	IN93	Dansyl
IN24	CH_2COOH	IN59	OPO_2H_2	IN94	Tosyl
IN25	CH_2COCH_3	IN60	ONO	IN95	Trifluoroacetyl
IN26	CH_2COPh	IN61	SCN	IN96	Acetoacetyl
IN27	CH_2OCOCH_3	IN62	NHCHO	IN97	9-fluoroenylmethoxycarbonyl
IN28	CH_2SO_2OH	IN63	SO_2Cl	IN98	Tetrahydropyranyl
IN29	$CH_2PO_3H_2$	IN64	OCH_3	IN99	9-Borabicyclo(3.3.1.)nonyl
IN30	$CHCH_2$	IN65	N_3	IN100	C5H10
IN31	CH_2CHCH_2	IN66	NC		
IN32	CCH	IN67	$NHSO_3H$		
IN33	CN	IN68	OSO_3H		
IN34	CF_3	IN69	SO_2CF_3		
IN35	CCl_3	IN70	$COCHCH_2NH_2$		

MATERIALS AND METHODS

Software

Computational Screening of all the proposed structures of Indolizine derivatives has been carried out using various computational tools such as ACD/Chemsketch 2024.1.4, Molinspiration, PASSOnline, SwissADME, Open Babel, AutoDock4, BIOVIA Discovery Studio 2025 as shown in the Table. All are installed in HP Laptop 15- fd0xxx with a 13th Gen Intel Core i5 processor and 16.0GB of RAM with Windows 11 as operating system.

Table.1 Softwares used in in silico Studies

SOFTWARE USED	USAGE
ACD/Chemsketch	To draw 2D Structure
Molinspiration	To calculate drug likeness property
PASSOnline	To Predict Bioactivity
SwissADME	To determine physicochemical properties
Open Babel	To convert sdf.file into Pdb.file
Autodock4	Docking
BIOVIA Discovery Studio	Visualizing

Molecular Docking Studies

Protein Preparation

The X-ray co-crystallized structures of wild type (PDB ID: 1KLM) and mutant type (PDB ID: 1JLB) proteins used in this study were obtained from Research Collaboratory for Structural Bioinformatics (RCSB). For every protein molecule, co-crystallized

hetatm, water molecule was deleted, added polar hydrogen. Assigned AD4 type and Kollman Charges and it was saved in PDBQT format.

Ligand Preparation

All the ligands were converted from SDF format to PDB format using Open Babel application. It is further prepared and converted in PDBQT format using Autodock4 software.

Receptor Grid Generation

Autogrid was used for generating specific grid maps for Indolizine derivatives. The generation of the grid box was done by taking the dimensions of the 3 coordinates (X,Y and Z) at 40 x 40 x 40 with spacing of 0.375 A°. The values of X, Y and Z centres where determined by crystallographic position of the native ligand.

Docking Protocol Validation

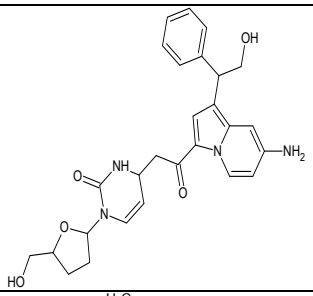
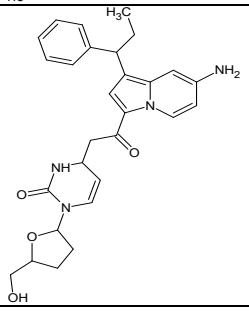
To carry out the docking procedure, the derived analogues were first docked into the active site of the target protein. Along with that, a standard drug was docked under identical parameters. The binding affinities of the analogues and standard drug were compared to identify the promising compound.

RESULTS

ACD/Chemsketch

Selected Indolizine Analogues are designed using ACD/Chemsketch including its Smile Notations shown in Table.2.

Table.2 Indolizine derivatives with Smile notatipn and IUPAC name

CODE	Structure	Smiles	IUPAC
IN1		O=C1NC(C=CN1C1CCC(O1)CO)CC(=O)c1cc(c2cc(N)ccn12)C(CO)c1ccccc1	2-(2-(6-amino-9-(hydroxymethyl)-5-phenyl-7H-pyrido[2,3-b]indol-7-yl)-2-oxoethyl)-3-(2-hydroxyethyl)-5-(pyrrolidin-1-ylmethyl)-1,3-diazinane-4,6-dione
IN2		O=C1NC(CC(=O)c2cc(c3cc(N)ccn23)C(CC)c2ccccc2)C=CN1C1CCC(O1)CO	2-(2-(6-amino-9-ethyl-5-phenyl-7H-pyrido[2,3-b]indol-7-yl)-2-oxoethyl)-3-(2-hydroxyethyl)-1,3-diazinane-4,6-dione

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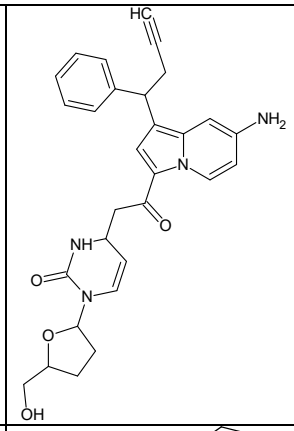
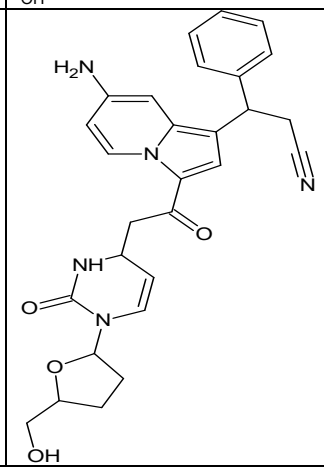
IN32		O=C1NC(CC(=O)c2cc(c3cc(N)ccn23)C(CC#C)c2ccccc2)C=CN1C1OC(CC1)CO	2-(2-(6-amino-9-(prop-2-yn-1-yl)-5-phenyl-7H-pyrido[2,3-b]indol-7-yl)-2-oxoethyl)-3-(2-hydroxymethyl-1,3-dioxolan-4-yl)methyl-1,3-diazinane-4,6-dione
IN33		O=C1NC(CC(=O)c2cc(c3cc(N)ccn23)C(CC#N)c2ccccc2)C=CN1C1CCC(O1)CO	2-(2-(6-amino-9-(cyanomethyl)-5-phenyl-7H-pyrido[2,3-b]indol-7-yl)-2-oxoethyl)-3-(2-hydroxyethyl)-1,3-diazinane-4,6-dione

Molinspiration

By performing Molinspiration, we came to know that out 100 Indolizine Analogues only 4 compounds fully comply with Lipinski's Rule of 5 and 12 analogues exhibited violation in Molecular Weight which is more than 5 were shown in Table.3.

Table.3 Results of Molinspiration

Sl NO	CODE	Log P	Molecular Weight	No. of Hydrogen bond acceptors	No. of Hydrogen bond donors	No of rotatable bonds	No. of violations
1.	IN1	1.93	490.56	9	5	8	0
2.	IN2	3.44	488.59	8	4	8	0
3.	IN32	2.99	498.58	8	4	8	0
4.	IN33	2.02	499.57	9	4	8	0

PASS Online

PASS was used to predict the biological activity of the following analogues by estimating their probability of Activity (Pa) and probability of Inactivity (Pi) were shown in Table.4.

Table.4 Results of PASS Online

Sl no	CODE	RNA directed DNA polymerase inhibitor	
		Pa	Pi
1	IN1	0,536	0,007
2	IN2	0,531	0,007
3	IN32	0,526	0,007
4	IN33	0,524	0,007

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Molecular Docking

Designed derivatives docked with wild type (PDB ID: 1KLM) and Mutant (PDB ID: 1JLB) proteins. The docked images of the analogues are shown Table.5 and 6 respectively.

Table.5 Docking images of proposed ligands with protein 1KLM along with docking score.

a) Wild Type (PDB ID:1KLM)

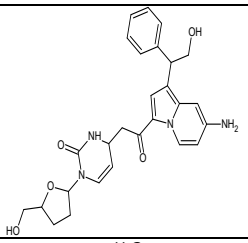
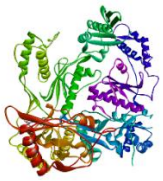
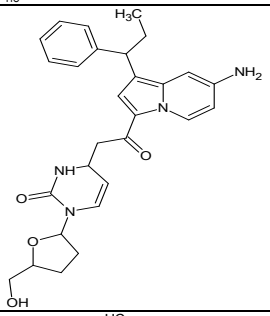
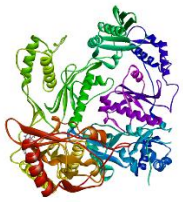
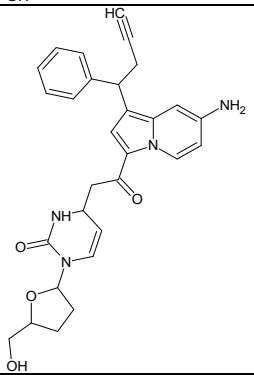
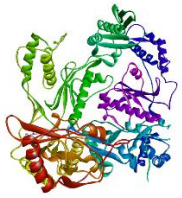
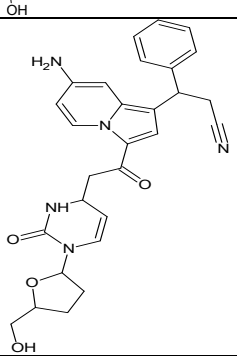
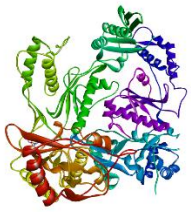
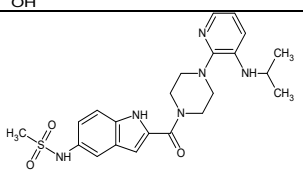
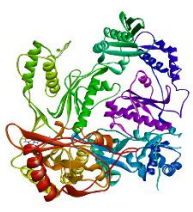
Sl no	CODE	STRUCTURE	PDB ID	DOCKING SCORE	LIGAND – PROTEIN COMPLEX
1	IN1		1KLM	-12.03	
2	IN2		1KLM	-11.05	
3	IN32		1KLM	-8.75	
4	IN33		1KLM	-11.02	
SD	Delavirdine		1KLM	-12.48	

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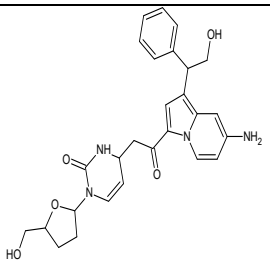
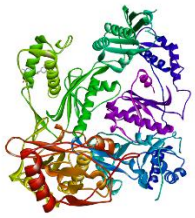
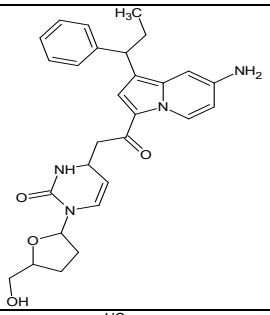
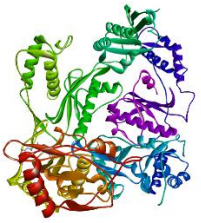
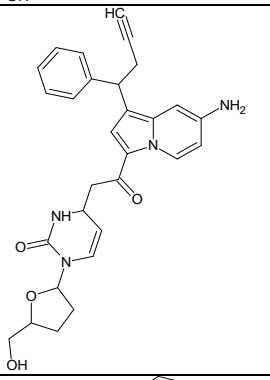
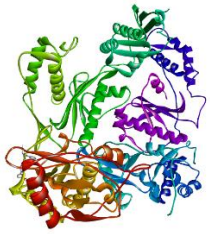
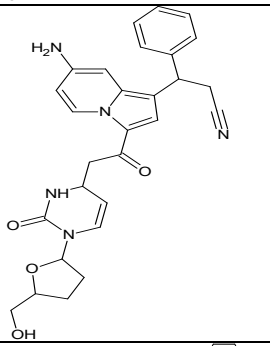
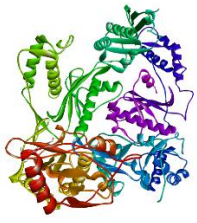
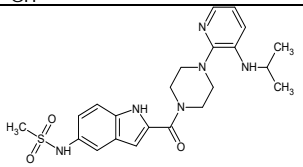
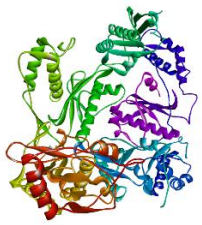
Table.6 Docking images of proposed ligands with protein 1JLB along with docking score.

b)Mutant type (PDB ID: 1JLB)

Sl no	CODE	STRUCTURE	PDB ID	DOCKING SCORE	LIGAND – PROTEIN COMPLEX
1	IN1		1JLB	-5.95	
2	IN2		1JLB	+22.85	
3	IN32		1JLB	+8.50	
4	IN33		1JLB	+29.72	
SD	Delavirdine		1JLB	+8.54	

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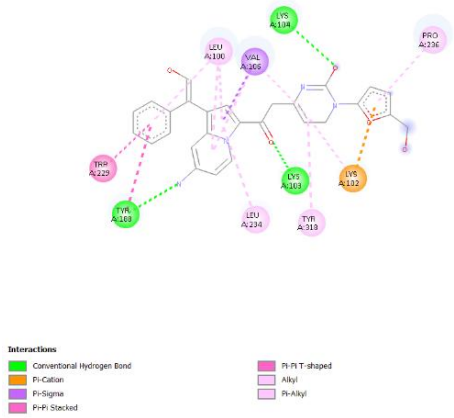
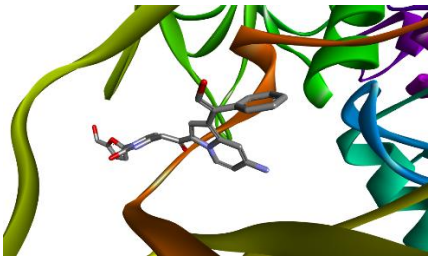
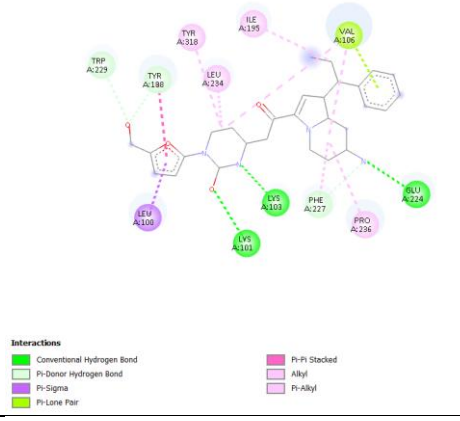
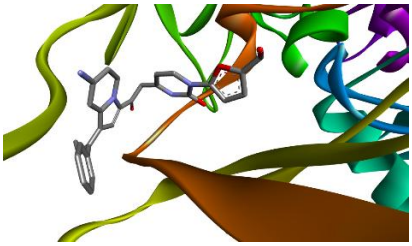
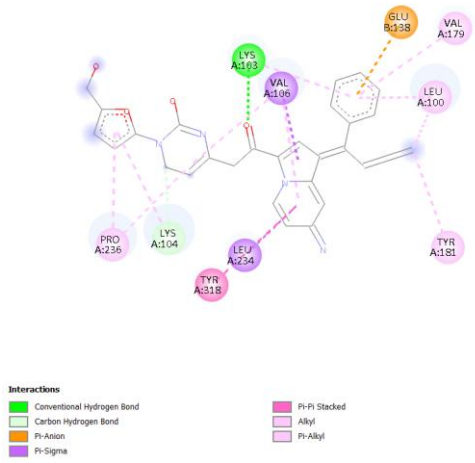
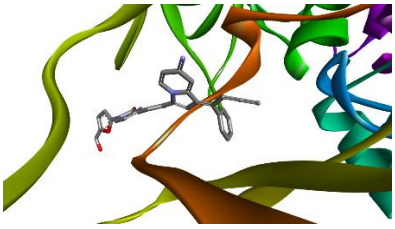
Protein – Ligand Interaction

2D images of protein - ligand interactions of selected derivatives with images of docked complex shown in Table.7 (1KLM) and Table.8 (1JLB).

Table.7 Docking complex of 1KLM with selected analogues along with their 2D images of interactions

a) Wild Type (PDB ID: 1KLM)

CODE	PROTEIN-LIGAND INTERACTIONS	PROTEIN-LIGAND COMPLEX
IN1		
IN2		
IN32		

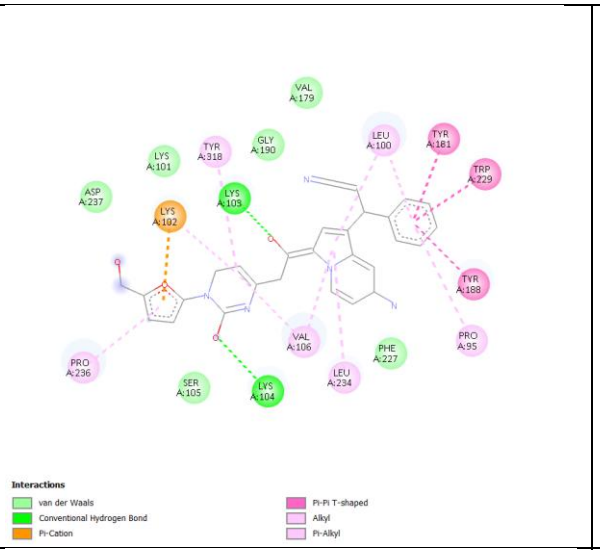
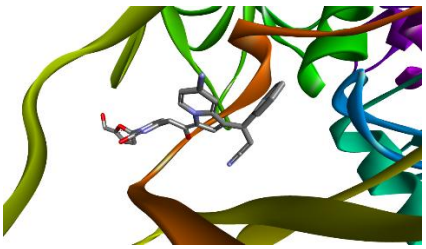
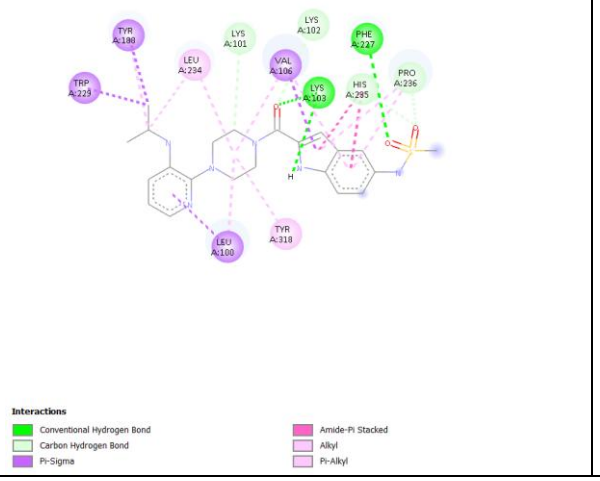
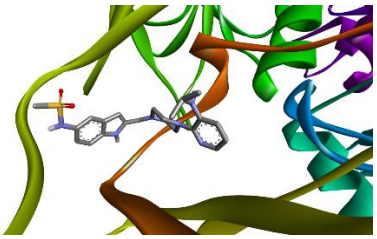
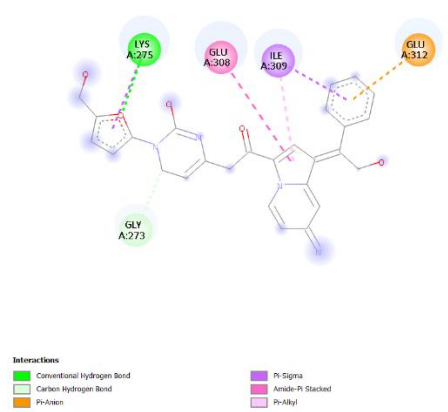
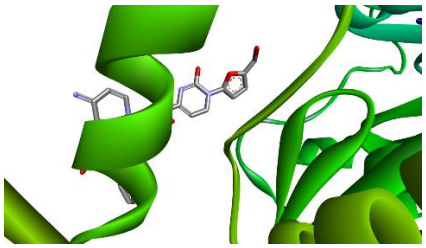
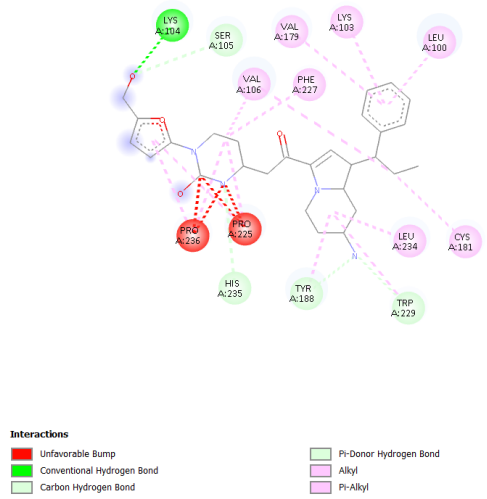
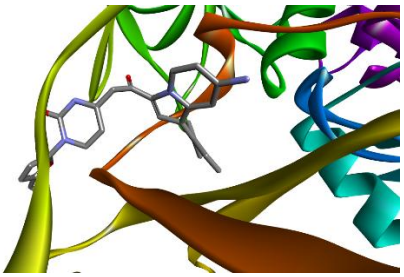
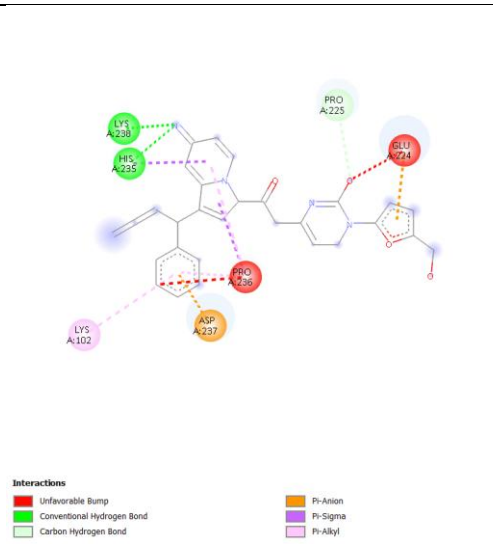
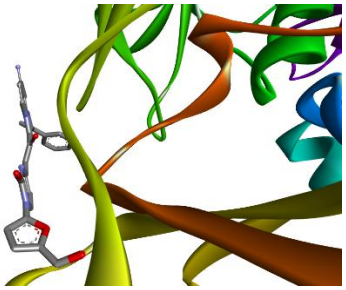
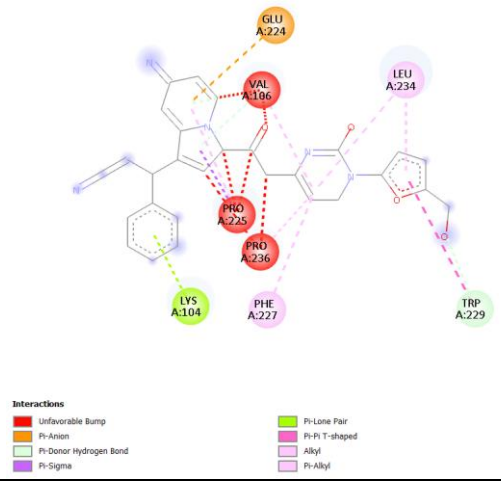
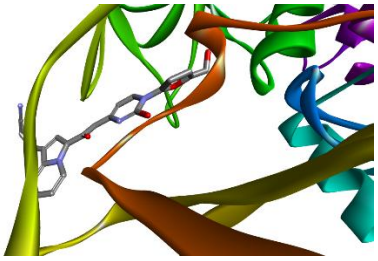
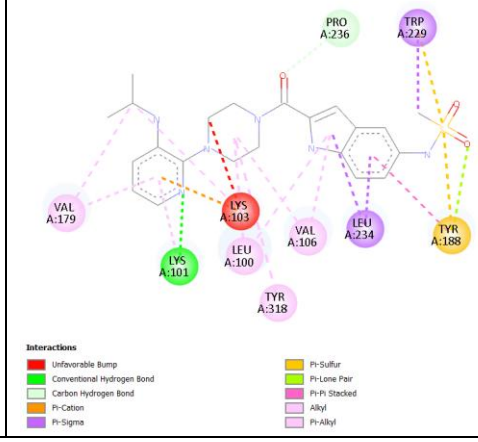
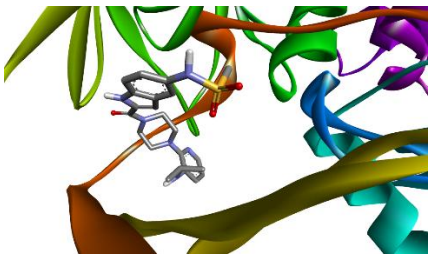
IN33		
SD		

Table.8 Docking complex of 1JLB with selected analogues along with their 2D images of interactions.

b) Mutant Type (PDB ID: 1JLB)

CODE	PROTEIN-LIGAND INTERACTIONS	PROTEIN-LIGAND COMPLEX
IN1		

IN2		
IN32		
IN33		

SD		

PHARMACOKINETIC AND TOXICITY EVALUATION OF SELECTED ANALOGUES

Using SwissADME, Pharmacokinetic evaluation has been done. Toxicity evaluation was done by using ADMET 3.0. ADME and Toxicity evaluation of selected compounds and standard drugs are shown Table.9.

Table.9 ADME & Toxicity evaluation of selected compounds docked with protein Reverse Transcriptase

CODE	Absorption	Distribution		Metabolism		Excretion		Toxicity	
		Vd	BBB	Inhibitor	Substrate	$T_{1/2}$	Cl		
IN1	GIT	0.202	No	Nil	P-gp	0.826	6.018	DILI	+
								R.T	-
								C.D	---
								DIN	++
IN2	GIT	0.132	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	P-gp	0.719	6.285	DILI	+
								R.T	++
								C.D	--
								DIN	+
IN32	GIT	0.101	No	CYP2C9, CYP2D6, CYP3A4	P-gp	0.763	5.287	DILI	-
								R.T	+++
								C.D	---
								DIN	++
IN33	GIT	0.155	No	CYP2C9, CYP2D6, CYP3A4	P-gp	0.789	5.126	DILI	++
								R.T	+++
								C.D	---
								DIN	-
Delavirdine	GIT	-0.227	No	CYP2C9, CYP2D6, CYP3A4	P-gp	0.501	5.259	DILI	+++
								R.T	++
								C.D	++
								DIN	+++

DILI: Drug Induced Liver Injury

RT: Respiratory Toxicity

CD: Cardiac Toxicity

DIN: Drug Induced Nephron Injury

The evaluated pharmacokinetic/ADME profile of the chosen indolizine derivatives (IN1, IN2, IN32, IN33) and Delavirdine indicates good oral absorption for all compounds, a moderate degree of distribution, and no predicted penetration across the blood-brain

barrier. The predictions for metabolism indicate that IN1 displayed no significant CYP450 inhibition while IN2, IN32, IN33 and Delavirdine are predicted to inhibit several CYP450 enzymes. Elimination characteristics (half-life, clearance) also suggest that these compounds would show an acceptable level of drug persistence in the body to allow for oral administration. The predicted toxicity values, converted using the classification probability scale (0-1 mapped to --- to +++), suggest that IN1 had low levels of toxicity, mild potential for drug-induced liver injury (+), little potential for respiratory toxicity (-), no significant potential for cardiotoxicity (---) and moderate potential for nephrotoxicity (++). IN2 exhibited slightly higher risk particularly for respiratory toxicity (++), while IN32 and IN33 demonstrated moderate levels of liver toxicity (++), higher levels of respiratory toxicity (+++) and moderate levels of nephrotoxicity (++). The predicted toxicity for Delavirdine was the highest across several endpoints including very serious liver injury (+++), respiratory toxicity (++), as well as very serious levels of nephrotoxicity (+++). Overall, these data indicate that IN1 and IN2 present reasonable pharmacokinetic and safety characteristics; moreover, the potential of these compounds, from a mesoscale perspective, to inhibit CYP450 enzymes is an essential consideration in further developing this class of compounds.

CONCLUSION

we designed 100 Indolizine analogues using ACD/Chemsketch. We then used Molinspiration to quickly calculate key drug- like properties, including log P, molecular weight, polar surface area, rotatable bonds and the number of H bond donor and acceptors. Out of 100 compounds, only 4 compounds met Lipinski's rule of 5, showing their suitability as orally active candidates. Pharmacological activities were predicted by PASS. The binding affinity of proposed ligands to the HIV Reverse Transcriptase were determined by AutoDock 4. They were subjected to pharmacokinetics and toxicity evaluation by SwissADME and ADMET Lab 3.0. Molecular docking studies were carried out for all the selected ligands against both wild type (1KLM) and mutant type (1JLB) proteins of HIV Reverse Transcriptase and we came to know that compounds IN1(both wild type and mutant type) and IN33 (wild type only) were identified as promising inhibitors. The results reveal that these compounds exhibit a greater property for the binding when compared to Standard drug such as Delavirdine. Thus, the newly designed drugs demonstrate potential as a novel class anti-viral agents with further research, may evolve into the effective Anti- Viral drugs.

REFERNCES

1. Sandeep C, Venugopala KN, Khedr MA, Attimarad M, Padmashali B, Kulkarni RS, Venugopala R, Odhav B. Review on chemistry of natural and synthetic indolizines with their chemical and pharmacological properties. *Mini Rev Med Chem.* 2019;19(14):1235–1258.
2. Sadowski B, Klajn J, Gryko DT. Recent advances in the synthesis of indolizines and their π-expanded analogues. *Org Biomol Chem*. 2016;14(33):7804–7828. doi:10.1039/C6OB00985A
3. da Silva TS, da Silva Souza M, Andricopulo AD, Coelho F. Discovery of indolizine lactones as anticancer agents and their optimization through late-stage functionalization. *RSC Adv*. 2023;13:20264-20270. doi:10.1039/D3RA03395C.
4. Dawood KM, Abbas AA. Inhibitory activities of indolizine derivatives: a patent review. *Expert Opin Ther Pat*. 2020;30(12). doi:10.1080/13543776.2020.1798402.
5. Huang W, Zuo T, Jin H, Liu Z, Yang Z, Yu X, Zhang L, Zhang L. Design, synthesis and biological evaluation of indolizine derivatives as HIV-1 VIF–ElonginC interaction inhibitors. *Mol Divers.* 2013;17(2):221–243. doi:10.1007/s11030-013-9424-3.
6. Chandra P, Ganguly S, Karmakar S. Comparative studies of various NNRTIs in the active site of different HIV-1RT receptors. *Chem Proc.* 2021;3(1):33. doi:10.3390/ecsoc-24-08313.
7. Tarasova O, Poroikov V, Veselovsky A. Molecular docking studies of HIV-1 resistance to reverse transcriptase inhibitors: mini-review. *Molecules*. 2018;23(5):1233. doi:10.3390/molecules23051233.
8. Ren J, Nichols C, Bird L, Chamberlain P, Weaver K, Short S, et al. Structural mechanisms of drug resistance for mutations at codons 181 and 188 in HIV-1 reverse transcriptase. J Mol Biol. 2001;312(4):795-805. doi:10.1006/jmbi.2001.4966.
9. Ren J, Milton J, Weaver K, Short S, Stuart DI, Stammers DK. Structural basis for the resilience of efavirenz (DMP-266) to drug resistance mutations in HIV-1 reverse transcriptase. J Mol Biol. 2000;301(4):915-927. doi:10.1006/jmbi.2000.3997.

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