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IDENTIFICATION AND ANALYSIS OF LEAD COMPOUNDS AGAINST HIV-1 INTEGRASE ENZYME USING ADMET PREDICTION AND DOCKING ANALYSIS

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Keywords:

Acquired immune deficiency syndrome, Human immunodeficiency Virus-1, HIV-Integrase, Docking, ADMET, ReCore, Lead compounds

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ABSTRACT: Acquired immune deficiency syndrome (AIDS), one of the most challenging diseases world-wide is caused by human immunodeficiency virus (HIV), member of human retrovirus family. Various therapies and treatments of HIV are provided, but these are rapidly drug resistance in recent decades. After the explosion of HIV integrase (enzyme essential for the replication of DNA virus in the host genome), pharmacoinformatic approaches have become necessary to find target proteins and potential lead compounds. In the current study, identification of novel lead compounds for the HIV-1 integrase enzyme is done using different chemometric techniques. A set of 26 compounds obtained from literature are used for the ADMET prediction using DruLiTo software. The FlexX score of the compounds C2 and C10, fitting all the ADMET properties, with the target protein is found to be - 8.0 and - 18.4 respectively. These ligands are further analysed for the core replacement studies using ReCore module of LeadIt software which gave two novel compounds from Zinc database qualifying the ADMET properties with FlexX score of - 10.3 for ZINC0358167 and - 12.2 for ZINC2184697 respectively. The docking score of lead compounds obtained from ZINC database are compared and found to be superior to that of the FDA approved drugs Raltegravir and Elvitegravir. The analysis of binding preferences and improvement of the inhibitory potency is done.

INTRODUCTION: Human immunodeficiency virus (HIV) is a lenti-virus belonging to the retrovirus family, which infects the immune system of the body and over time causes acquired immune deficiency syndrome (AIDS) [1]. AIDS has produced a crucial health crisis.

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The HIV virus is transferred from an infected person to normal people through the medium of unprotected sexual intercourse, contaminated medical equipment, bodily fluids and vertical infection (pregnancy, delivery, or breast feeding) [2, 3]. HIV destroys the human immune system which is carried out in seven stages. Three enzymes are used for HIV infections *i.e.* reverse transcriptase (RT), protease (PR) and integrase (IN). The role of HIV reverse transcriptase allows to convert the single stranded RNA of the virus into the double stranded DNA. The enzyme integrase allows the integration of the viral DNA into the host genome.

After the integration, HIV protease cleaves newly synthesized polyproteins into the mature protein. These enzymes are majorly target for the amelioration of novel anti-HIV drugs [4]. Two types of HIV are found, *i.e.* HIV-1 and HIV-2, in which HIV-1 cause of the majority of HIV infections globally and less infectivity of HIV-2 is found in Western Africa. HIV is incurable and soon causes death. According to statistics of the World Health Organization (WHO), 36.7 million people are living with HIV in worldwide at the end of 2015. Currently, FDA has approved anti-HIV drugs in clinical use such as non-nucleoside reverse-transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); and nucleoside reverse-trans-criptase inhibitors (NRTIs). Combination therapies like (highly active antiretroviral therapy) HAART is using different inhibitors provided for the best clinical outcomes. The above inhibitors are widely used for human who suffered from HIV infection, but these are ineffective to remove the HIV infection [5].

HIV integrase is a multi-domain and 32KDa enzyme which is responsible for the integration of viral DNA in a two-step reaction: In the first step, two nucleotides are removed from each 3-end of the viral DNA, this reaction called as 3-end processing. In the next step, a pair of viral DNA ends is inserted into the target host DNA, this reaction called as trans-esterification reaction. This enzyme subsists of three domains: the N-terminal domain (NTD), the catalytic core domain (CCD) and the C-terminal domain (CTD) [6], shown in **Fig. 1** [7].

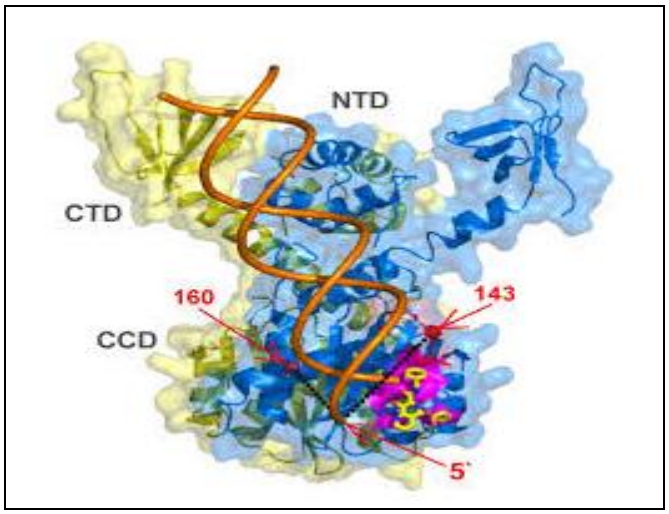


FIG. 1: CATALYTICALLY-ACTIVE COMPLEX OF HIV-1 INTEGRASE

LEDGF (lens epithelium-derived growth factor) is a transcriptional co-activator which binds to HIV-1 integrase through extreme development-conserved integrase binding domain (IBD) [8]. The drugs which is approved by FDA, *i.e.* Raltegravir (RAL); Elvitegravir (EVG), Dolutegravir (DTG) in clinical use. These drugs contribute an identical process of action at the binding active site of integrase and inhibit the strand transfer (ST) activity [9, 10]. Raltegravir is the first drug for targeting HIV-1 integrase in 2007 and Elvitegravir is created in 2012 but these drugs have rapid exposure of resistance mutations and made by the three recognized great resistance pathways [11]. In this study, HIV-1 integrase inhibitors are examined for the development of new drug molecules for surviving the humans.

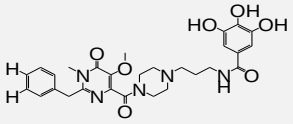
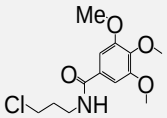
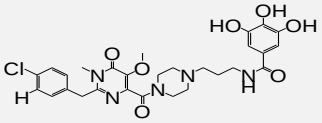
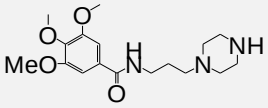
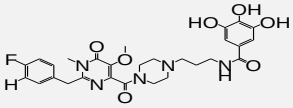
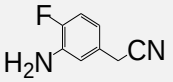
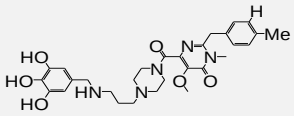
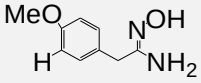
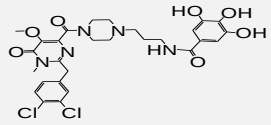
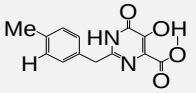
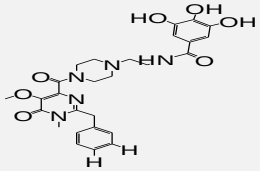
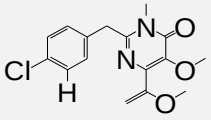
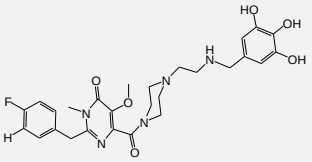
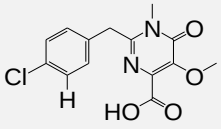
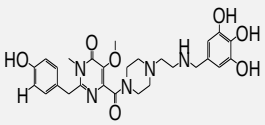
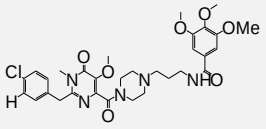
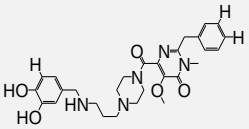
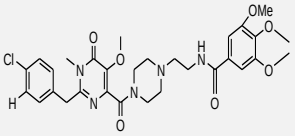
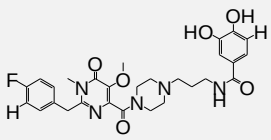
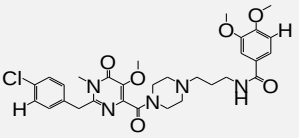
Drug design is the process of creating of new medicines depends on the cognition of biological targets. It is very complex, prolonged and very extravagant process, but it requires a lot of struggle, patience to lead a new drug molecule to the pharmaceutical industries. This new drug should be tested in pre-clinical and clinical trials. The drug is most commonly an organic small molecule which can be used to activate or inhibit the functions of a bio molecule such as a protein, which results the discovery and improvement of new active compounds for therapeutic benefit to the patient [12]. There are various methods which can be used for the development of drugs such as QSAR, virtual screening, molecular docking, pharmacophore, prediction of physical, chemical and biological properties of the molecules [13, 14]. The study examined that the prediction of new active compounds using molecular docking, ADMET properties, ReCore for the HIV-1 integrase inhibitors which are useful in drug designing.

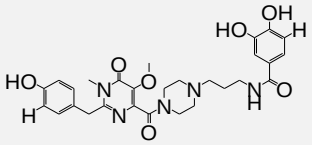
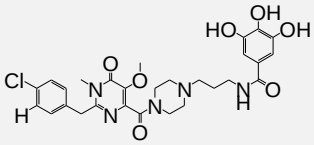
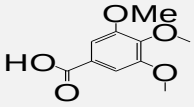
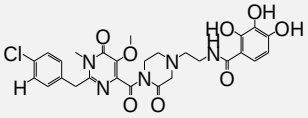
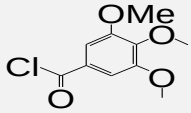
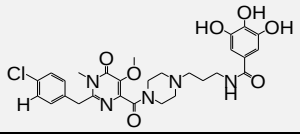
MATERIALS AND METHODS:

Dataset / Ligand Preparation: Three dimensional coordinates of 26 ligands taken from literature [15], their isomeric, ionization and tautomeric states generated using chemdraw ultra software (www.cambridgesoft.com), USA. It is a comer-cially available software package developed by Cambridge Soft and used widely in chem-informatics and drug designing for generating chemical structure for ligand based studies.

It is most extensive and powerful tool that assists the conversion of chemical structure to chemical name or vice versa, structure cleanup and structure formation easily. Structure files are generated in various formats such as ".mol" and ".cdx" extension [16]. The structure and Log P of the ligands considered in this study are shown in **Table 1**. These ligands are converted into SMILES (Simplified Molecular Input Line Entry Specification) format. SMILES refer to line notation for encoding molecular structure and widely used as a general purpose chemical nomenclature. It represents the compound very compact and gives the correct information about bond, connect, valence and chirality [17]. Furthermore, Open Babel is used for the compounds to the proliferation of multiple chemical file formats. It introduces 2D and 3D geometries which can be carried out to manipulate chemical data, such as organic chemistry, drug design, materials science and computational chemistry. The Open Babel is used to convert ".mol" file into ".mol2" file [18].

TABLE 1: STRUCTURE OF TRIHYDROXYLATED AROMATIC DERIVATIVES

S. no.	Structure	LogP	S. no.	Structure	LogP
C1.		2.2	C14.		2.0
C2.		1.3	C15.		1.6
C3.		1.1	C16.		2.4
C4.		2.8	C17.		1.3
C5.		1.3	C18.		1.3
C6.		1.9	C19.		1.3
C7.		1.0	C20.		1.6
C8.		0.1	C21.		0.1
C9.		3.0	C22.		1.0
C10.		1.7	C23.		1.4

C11.		0.7	C24.		4.2
C12.		1.3	C25.		2.9
C13.		0.7	C26.		1.7

Protein Preparation: The Protein Data Bank (PDB) is used to download the target proteins. HIV-1 integrase catalytic domain is retrieved from the Protein data bank (PDB id: 1QS4) [19]. Chain A is chosen for ligand binding among chain A, B and C and all water molecules were removed from the complex. The protein is prepared using the LeadIt toolkit.

ADMET Prediction: ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. The prediction of the ADMET properties plays an important role which can be applied in the drug design process. ADMET has allowed a complementary approach that is blending elements of quantitative structure property relationships along with the major protein structure-based view. The combinations of in vivo and *in vitro* predictions help to reduce the number of safety problem by using computational ADMET. Computed physic-chemical properties are associated with chemical compounds that have good oral bioavailability, less or no toxicity and optimum values of physicochemical properties are key parameters for the anti-HIV drug discovery. Pharmaceutical industry observes large attrition rates of preclinical and clinical candidates due to toxicity or lag of optimal pharmacokinetics properties that have a consequence in high costs and increased timelines for the drug discovery process [20]. ADMET related physicochemical properties for 26 lead compounds derived anti-HIV 1 integrase are predicted using Drug Likeness Tool (DruLiTo) software. Drug likeness is the tools which can be freely available package for the prediction of toxicity examined the physico-chemical properties like Lipinski's rule, Veber rule, BBB rule and Quantitative Estimate of Drug-likeness (QED) [21].

Furthermore, the best anti HIV-1integrase drug explained various physicochemical properties of compounds such as log P, log D, TPSA, MW, log S, HBA, HBD and nRot for the high probability of clinical success [22]. The threshold values of Lipinski rule, Veber rule, BBB as well as the quantitative estimate of drug-likeness (QED) are also calculated using drug- likeness tool are shown in **Table 2**.

TABLE 2: PHYSICOCHEMICAL PROPERTIES AND THEIR THRESHOLD VALUES

S. no.	Properties	Rules	Threshold Value
1.	Molecular weight	Lipinski's BBB	<=500 <=400
2.	LogP	Lipinski's	<=5
3.	HBD	Lipinski's	<=5
4.	HBA	Lipinski's	<=10
5.	PSA	Veber	<=140
6.	UnWQED	Unweighted	>=0.5
7.	WQED	Weighted	>=0.5

Molecular Docking: Molecular docking is a key tool which can be used in structural molecular biology and computer-assisted drug design. The goal of docking is to conclude that the lead binding mode of a ligand with a protein of known three-dimensional structure. Protein-ligand docking is an effective method that defines to search for exact ligand conformations within a targeted receptor when the structure of proteins is known and it is analysed the calculation of scoring functions for prediction of binding free energies. For the purpose of visualising molecular interactions the 3D structures of HIV-1 integrase inhibitors are generated using ChemDraw ultra software package [23] and 3D structure of protein molecule is taken from the Protein data bank (PDB id: 1QS4). There are no conformational changes in rigid docking interactions while in flexible docking interactions there are possibilities of conformational changes between proteins [24].

All of the docking programs are capable to develop ligand conformations and crystallography is able to intend protein ligand complex structures for at least one of the targets.

FlexX is fast, flexible docking tool that uses an Incremental Construction (IC) algorithm to place the ligand into the active site for scoring the structures and offers automatic ligand positioning [25]. For docking studies, the structure of ligands is transformed into a "SMILES" and "mol 2" format and legends are generated. A proteins description file is prepared by the FlexX graphic interface and the binding pocket of the reference ligand is taken as the active site for evaluating the molecular interactions between ligands and receptor.

ReCore Analysis: ReCore is a new fragment replacement tool and commercial available from Bio solve LeadIt for fast searching conformations of protein-ligand structures. It maintains 3D core replacement, fragment linking, growing and merging for active chemical scaffold hopping [26]. Furthermore, the filtering resultant structure is scored to suit the structure through the size of the fragment or various geometric properties [27].

RESULTS AND DISCUSSION:

ADMET Prediction: ADMET properties are needed to define the aggregate value to suitable the compounds for drug designing. 26 lead compounds are evaluated for drug design and development such as, molecular weight (MW), lipophilicity *i.e.* calculated partition coefficient (log P), algorithm partition coefficient (alogP), hydrogen bond acceptor (HBA), hydrogen bond donors (HBD), topological polar surface area (TPSA), number of rotatable bonds (nRB), number of atom (nAtom), number of acidic group (nAG), number of rigid bond (nRigidB), number of aromatic ring (nAR), number of hydrogen bond (nHB) and SAlerts (SA). The calculated physicochemical properties value for the drugs and leads compounds are mentioned in **Table 3**. The MW value of the drugs from 444 to 446, while MW value for lead compounds 143 to 586. The log P value of the drugs ranges between 1.6 and 1.9 while that of lead molecules ranges from 0.1 to 4.2.

TABLE 3: IMPORTANT COMPUTED PHYSICOCHEMICAL PROPERTIES OF LEAD COMPOUNDS AND DRUGS

S. no	MW	lnP	AlogP	HBA	HBD	TPSA	TPSA	nRB	nAtom	nAG	RC	nRigidB	nAR	nHB	SA
C1	517.9	2.2	-3.7	9	0	82.5	96.8	11	40	0	4	32	2	9	2
C2	552.9	1.3	-3.0	9	0	82.5	102.4	11	41	0	4	33	2	9	2
C3	536.9	1.1	-3.3	9	0	82.5	97.7	11	41	0	4	33	2	9	3
C4	513.9	2.8	-2.9	8	0	65.4	102.9	11	40	0	4	32	2	8	2
C5	587.9	1.3	-2.3	9	0	82.5	108.0	11	42	0	4	34	2	9	2
C6	505.9	1.9	-3.5	9	0	82.5	93.9	10	39	0	4	32	2	9	1
C7	508.9	1.0	-2.8	8	0	65.4	95.3	10	39	0	4	32	2	8	3
C8	505.9	0.1	-3.7	8	0	65.4	97.0	10	39	0	4	32	2	8	2
C9	485.9	3.0	-3.1	8	0	65.4	94.8	11	38	0	4	30	2	8	2
C10	520.9	1.7	-2.8	9	0	82.5	95.1	11	40	0	4	32	2	9	3
C11	517.9	0.7	-3.7	9	0	82.5	96.8	11	40	0	4	32	2	9	2
C12	552.9	1.3	-3.0	9	0	82.5	102.4	11	41	0	4	33	2	9	2
C13	199.9	0.7	-0.3	2	0	44.7	29.1	4	15	0	1	11	1	2	0
C14	588.9	2.0	-1.8	9	0	110.2	116.7	14	44	0	4	33	2	9	2
C15	576.9	1.6	-1.5	9	0	110.2	113.7	13	43	0	4	33	2	9	1
C16	560.9	2.4	-1.7	9	0	100.9	109.3	13	42	0	4	32	2	9	2
C17	552.9	1.3	-3.0	9	0	82.5	102.4	11	41	0	4	33	2	9	2
C18	556.9	1.3	-3.1	10	0	99.5	99.6	10	41	0	4	34	2	10	2
C19	218.9	1.3	0.2	1	0	44.7	33.0	4	15	0	1	11	1	1	1
C20	268.9	1.6	-0.3	2	0	44.7	47.3	8	19	0	1	11	1	2	1
C21	309.9	0.1	-1.4	4	0	48	66.7	9	24	0	2	16	1	4	1
C22	143	1.0	-0.2	2	0	23.7	15.8	1	11	0	1	10	1	2	1
C23	168	1.4	-0.6	1	0	21.5	22.8	3	13	0	1	10	1	1	3
C24	259.9	4.2	-0.4	6	0	55.7	46.9	4	20	0	2	17	1	6	3
C25	302.9	2.9	0.0	5	0	51.1	62.5	5	22	0	2	18	1	5	1
C26	294.9	1.7	-0.4	6	0	58.9	53.0	4	21	0	2	18	1	6	1
Raltegravir	444.1	1.6	-0.4	11	3	145.0	112.9	8	53	0	3	26	2	14	2
Elvitegravir	446.1	1.9	0.6	6	1	89.9	120.1	7	53	0	3	26	2	7	2

The alog P value range for the drug molecules varied from -0.4 to 0.6 and for lead compounds range from -3.7 to 0.2. TPSA ranges from 89.9 to 145.0 for the drugs while 21.5 to 110.2 for lead compounds.

Molecular Docking: The purpose of docking study is to generate the appropriate binding orientations and conformations of 26 highly active compounds. Flexible docking of these compounds is carried out on the active site of the HIV-1 integrase. The best docked and most reliable confirmations of compounds C2 and C10 are selected on the basis of expressing data shown in **Fig. 2** and **3**.

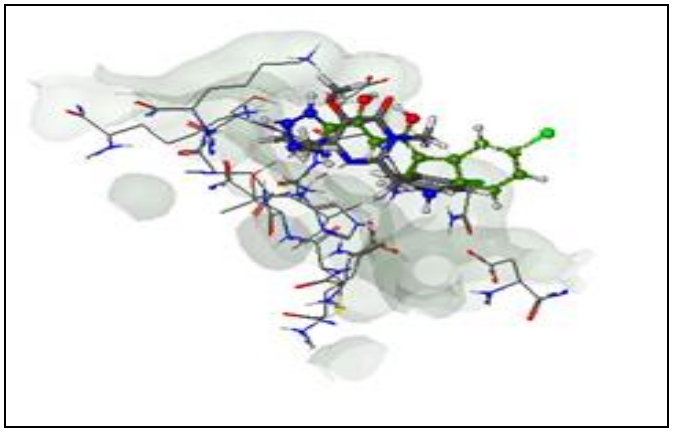


FIG. 2A: STEREO VIEW OF INTERACTIONS BETWEEN 1QS4 RECEPTOR PROTEIN AND LIGAND C2

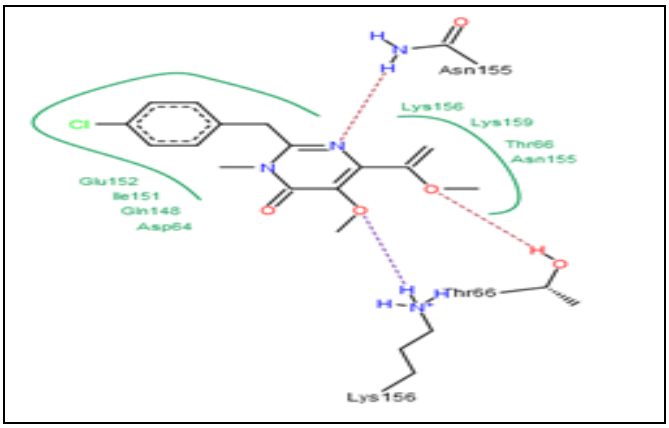


FIG. 2B: POSE VIEW DIAGRAM OF INTERACTION BETWEEN 1QS4 RECEPTORS PROTEINS AND LIGAND C2

The docked conformation of compounds revealed that the compounds interacted with binding pocket residues (HIS67, LYS159, THR66, ASN155, GLU152, LYS 156, GLN148, CYS65) of target protein 1QS4. The oxygen atoms of the ligand C2 shows hydrogen bond interactions with the H atom of terminal amide group of the LYS156 and H atom of terminal hydroxyl group of THR66 residues in the binding pocket respectively.

The H atom of the terminal amide group of the ASN155 residue interacts with N atom of ligand C2 as shown in **Fig. 2(a)** and **(b)**, whereas the H atom of HIS67 and LYS159 residues forms Hydrogen bonds with the oxygen atoms of the carboxylic group of the ligand C10 and H atoms of ASN155 and THR66 residues interacts with the O atoms of hydroxyl group of C10 as shown in **Fig. 3(a)** and **(b)**. The residues THR66 and ASN155 are found to be most probable site of binding of the ligands with the receptor.

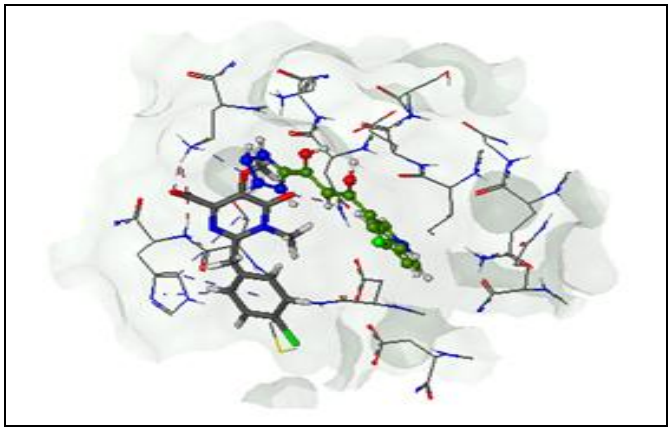


FIG. 3A: STEREO VIEW OF INTERACTIONS BETWEEN 1QS4 RECEPTOR PROTEIN AND LIGAND C10

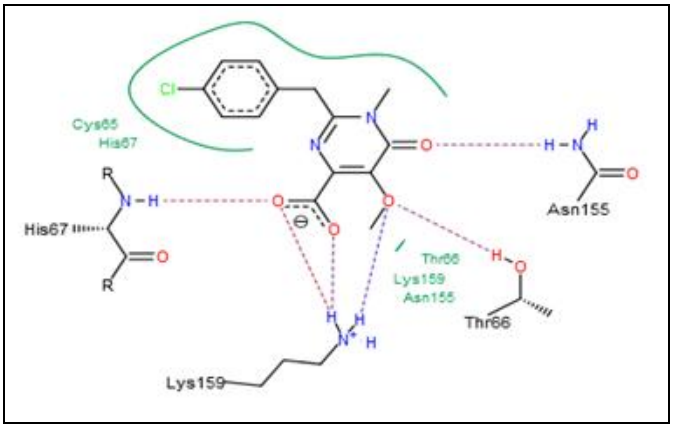


FIG. 3B: POSE VIEW DIAGRAM OF INTERACTION BETWEEN 1QS4 RECEPTORS PROTEINS AND LIGAND C10

ReCore Analysis: The ReCore module of Lead it is used for replacing the core of the best docked ligands C2 and C10 to obtain novel and more potent ligands which can be further modelled as anti HIV drugs. The ReCore module replaces the core of the input molecules and gives the best fitted molecule from the zinc database [28] with their

respective docking score for the receptor. Two ligands ZINC03581672 and ZINC02184697 selected on the basis of FlexX score after the core replacement are further used for the ADMET prediction.

The FlexX score of ligand with Zinc ID ZINC03581672 obtained from ReCore of C2 and ligand with Zinc ID ZINC02184697 obtained from ReCore of C10 are found to be -10.3 and -12.2 respectively. These ligands are further docked using Swiss dock (http://swissdock.vital-it.ch/) to confirm all the binding models of interactions. ASN155 and THR66 residues of the active site are showing H bond interaction with the newly identified compound ZINC03581672 on the receptor as shown in **Fig. 4a** and **b**. Similar interactions are observed on docking ZINC-02184697 on receptor binding pocket as observed in **Fig. 5a** and **b**. The statistical scores of the study are elucidated in **Table 4**.

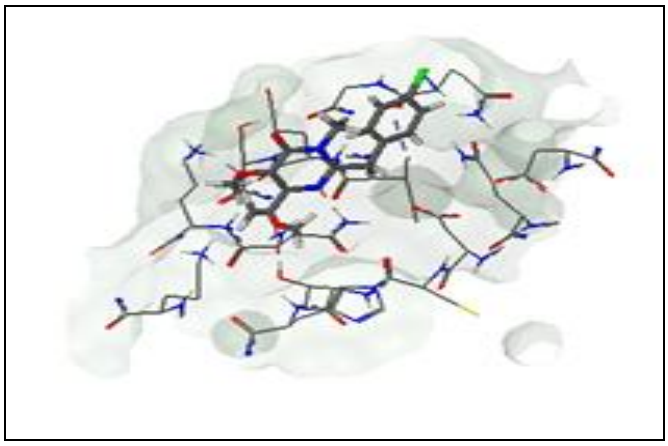


FIG. 4A: STEREO VIEW OF INTERACTION BETWEEN 1QS4 RECEPTORS AND LIGAND C2 BY USING RECORE STUDIES

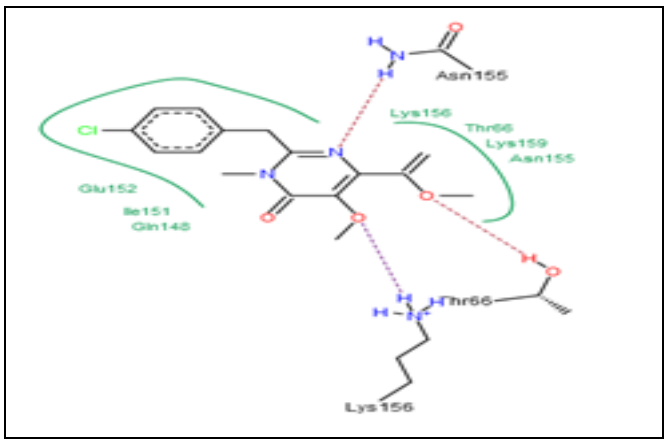


FIG. 4B: POSE VIEW DIAGRAM OF INTERACTION BETWEEN 1QS4 RECEPTORS PROTEINS AND LIGAND C2 BY USING RECORE STUDIES

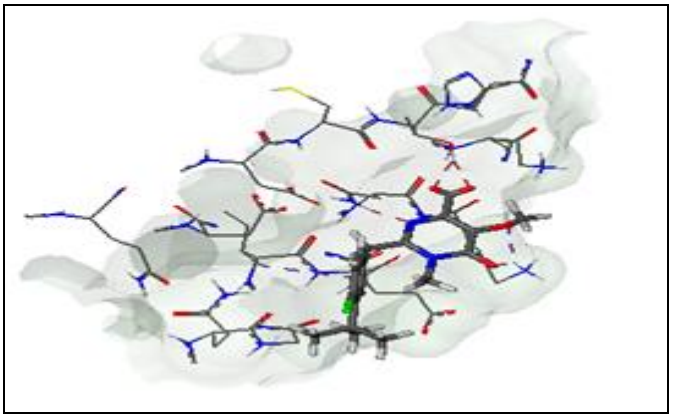


FIG. 5A: STEREO VIEW OF INTERACTION BETWEEN 1QS4 RECEPTORS AND LIGAND C10 BY USING RECORE STUDIES

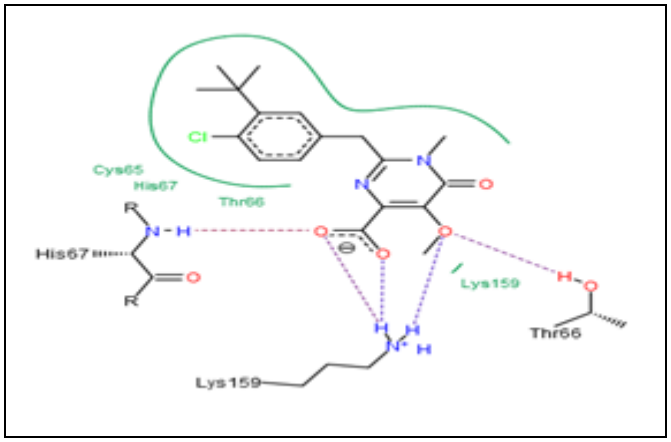


FIG. 5B: POSE VIEW DIAGRAM OF INTERACTION BETWEEN 1QS4 RECEPTORS PROTEINS AND THE LIGAND C10 BY USING RECORE STUDIES

TABLE 4: COMPARISON OF DOCK SCORE BETWEEN DRUG MOLECULES AND LEAD COMPOUNDS USING LEADIT FLEXX AND SWISSDOCK

Ligand	LeadIt	Swissdock
C2	-8.05	-7.4
C10	-18.5	-8.3
ZINC03581672	-10.3	-7.5
ZINC02184697	-12.2	-7.9
Raltegravir	Not Docked	-7.9
Elvitegravir	-3.19	-8.7

The two interactions such as ASN155 and THR66 are found as essential for these molecules to bind with the active site of HIV-1 integrals. At present, ASN155 residue provides the binding of ligands C2 and C10 in HIV-1 integrase for 3 prime processing activities and the same residue was found as the main target in previous literatures also. These ligands are found at most likely active site for target protein and used to calculate their FlexX score using ReCore. After the comparative analysis of the ligand-protein interaction of newly identified compounds with approved drugs Raltegravir

(ZINC013831130) and Elvitegravir (ZINC-013682481), the inhibitory potency along with FlexX score have been improved. Both the ligands obtained from ZINC database can be further modified and analyzed to design new compounds which can be exploited in the drug designing against HIV-1 integrase.

CONCLUSION: In the current study, we have analyzed the inhibitive nature of potent ligand molecule against crystalline structure of HIV-1 integrase. From the ADMET prediction and Docking analysis of all the ligands with target protein (PDB ID – 1QS4), it is found that ligands C2 and C10 can be potent ligand molecules as they are showing hydrogen bond interaction with most important and common residues ASN155 and THR66 at the active site of the target receptor with acceptable binding energy and FlexX score. Also, we have performed the ReCoremodeling of the best docked ligands and obtained two lead molecules from the zinc database with Zinc ID ZINC-02184697 and ZINC03581672 qualifying the ADMET properties and acceptable docking scores.

On comparing the results of docking analysis between newly identified lead compounds and target with approved drug compounds Raltegravir and Elvitegravir, it is observed that the new ligands have qualified Lipinski criteria and hence it has given optimum binding affinity and better binding energy along with FlexX score. Thus, this type of molecular scaffold can be exploited for the development of novel HIV-1 integrase inhibitors. This research on lead compound Zinc ID 02184697 and 03581672 will have to undergo toxicity test and pre-clinical trials and various optimization process before it can be eligible for clinical trials. Both of these ligands can be further modified and analysed to design new compounds which can be used as drug molecules against HIV-1 integrase.

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