Molecular association between HIV-1 Reverse Transcriptase (RT) Inhibitors and 3DLK Receptor

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Abstract
Research was done for obtaining the potent Human immunodeficiency virus-1 reverse transcriptase inhibitors (HIV-1 RTI) within minimum energy conformation (s) to treat retroviral HIV infection, acquired immunodeficiency syndrome (AIDS) and other sexually transmitted disease (STD) through cost effective rapid drug design technology. Therefore, one hundred twenty analogues were docked on 3DLK protein. H-97, H-95 and H-44 were found highly potent as HIV-1 non-nucleoside reverse transcriptase inhibitors (HIV-1 NNRTI) that would possibly halt HIV-1 for infecting host cell by blocking reverse transcription.

Key Words
Molecular docking, Protein-ligand docking, Acquired immunodeficiency syndrome (AIDS), Human Immunodeficiency Virus (HIV), HIV-1 reverse transcriptase (HIV-1 RT), Inhibitors, Drugs, Receptor proteins, Amino Acids and Active site.

1 INTRODUCTION
Drug is a recognized medicinal substance that administered to living body system to produce primary effect (desired therapeutic effect), use in clinical diagnostic tests and treatment of prompt medical conditions [15, 22, 48]. Current research was done for obtaining the potent anti-AIDS (anti-HIV-1 RT) drug (s) within minimum energy conformation (s) to treat sexually transmitted disease (STD) acquired immunodeficiency syndrome (AIDS) or retroviral HIV infection through cost effective molecular docking technology. AIDS is caused by human immunodeficiency virus (HIV), [7, 13, 18, 20]. The HIV (Genus *lentivirus*, family *Retroviridae* and group VI) infects CD4 cells, macrophages, or dendrite in human immune system and caused a severe cluster of multiple opportunistic infections, simple to complex or symptomatic to a symptomatic for many years with development of AIDS. It transmits through HIV/STD/STI positive infected male genital route (rectal) or female genital routes (vaginal or anal), oral sexuality (expose to infected lesion on lips or into mouth), infected mother to child (unborn), HIV positive mother's lection to new born or infants, un-tested blood transfusion, exchange of infected needles, surgical instruments, saloon and tattoo pricing tools. AIDS would not get by sharing hands, glassware, hugging, bath sanitary, insects (fire flyer, flyer, mosquito and cookroge) and saliva (salivary acids kills virus), [40, 50, 53, 65]. Up till now, 25 million people including 3, 30,000 children have died and 33.4 million people are having AIDS since 1981. Therefore, many

anti-AIDS medicines (reverse transcriptase inhibitors, protease retroviral inhibitors and integrase inhibitors) [6, 23] are available as treatment (delay in disease's progression or long lasting patient's survival). In this study, one hundred twenty 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio) (thymine)] (HEPT) analogues [33, 57](HIV-1 non-nucleoside reverse transcriptase) [2, 32] were docked on 3DLK (E.C. 2.7.7.49) protein by using SYBYL [51, 64], GOLD, [5, 8, 27, 36, 59, 60, 61] and MOE 1, [35, 41, 47, 49, 54] to obtained potent anti-AIDS or anti-HIV drugs with in bioactive conformations for combating life threaten retrovirus. Everyone knows that the drugs or inhibitors were patented through lengthy rotations from discovery to approval after burnt of money and time with no solution for bio-availability, toxicity and instability. But now advancements in drug design techniques and molecular docking packages have made the way very feasible, [3, 10, 12, 43, 52]. Docking is molecular associations between bioactive ligand (drug or drug like compound) and receptor (proteins or nucleic acids) that are essential for signal transduction pathway to form bio-molecular complex and predict binding affinity via docking parameters, [5, 11, 19, 26, 39]. It is also use to bind drug with receptor, to analyze molecular interaction, accelerate or block bioactivity, make the drug act like agonist or antagonist in biological pathways, scan databases for potent drugs, score best fit conformations and make them useful against clinical disorders. In other words, molecular docking is an important class of structure based drug design, [4, 9, 14, 21, 25, 29, 30] that constructs ligands within catalytic site of receptor, calculate lowest binding energy between interacted atomic groups and finally find out possible conformation of potent drug, [55, 58, 62]. The mechanic's of docking is like induced fit or like lock & key models that can simulate molecular recognition patterns and optimize conformations with minimal free energy by using genetic algorithms, Monte Carlo search, fragment based loops, point complementary protocol, distance geometry functions, scoring and flexibility parameters [37, 44, 46, 54, 63]. Geometric matching and molecular simulation control the complementary shape surfaces; simulate mechanics of docking by separating protein from its ligand by creating distance, rotation and sum up binding energy [16, 17, 31] in suitable conformation respectively. While Gold docking package for single or cluster docking within catalytic region can locate potent drugs in bioactive low energy [38, 45] conformations via dock ligand into receptor by using strings, scoring, computing molecular interaction energies for determine new ligand in bioactive conformations. Whereas, the molecular operating environment (MOE) is useful to design a drug for medicinal use by quantitative molecular vectors system.

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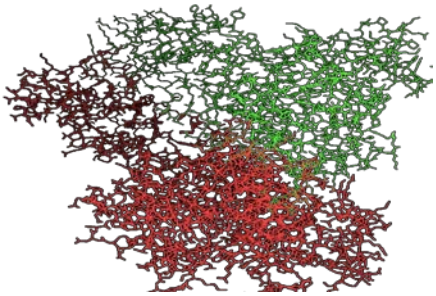
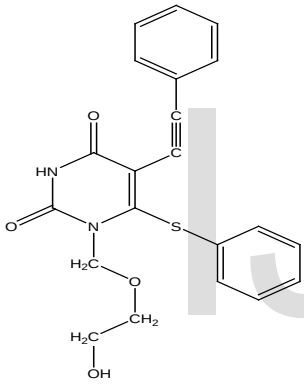
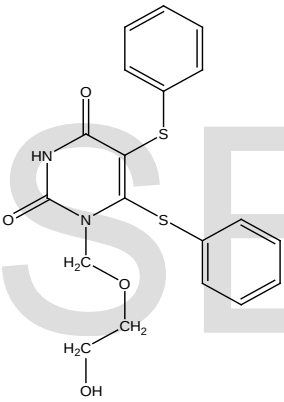
2 FIGURES



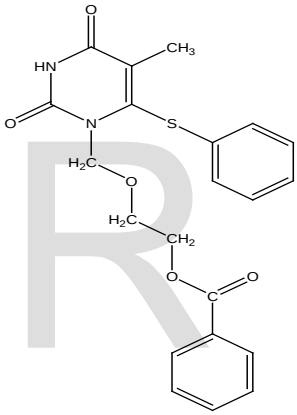
HIV-1 RT RECEPTOR PROTEIN (3DLK)



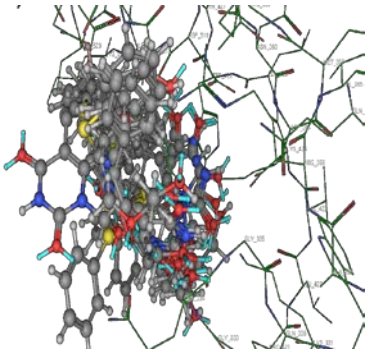
H-97

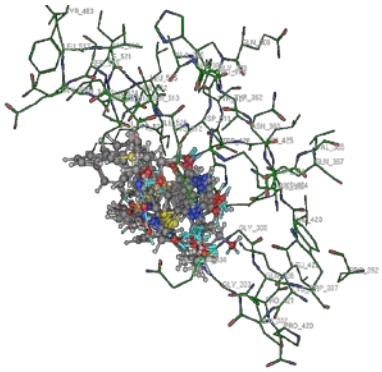


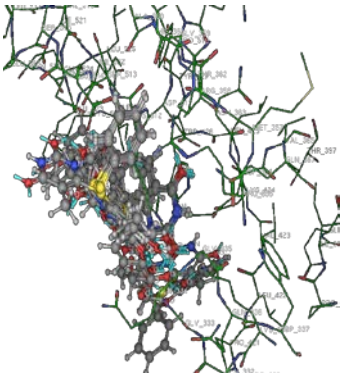
H-95

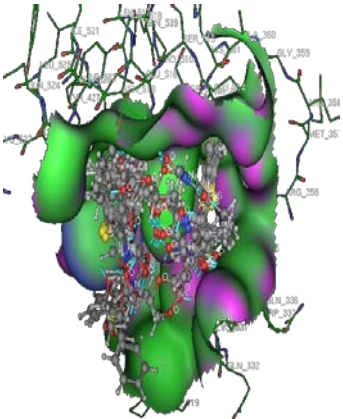


H-44









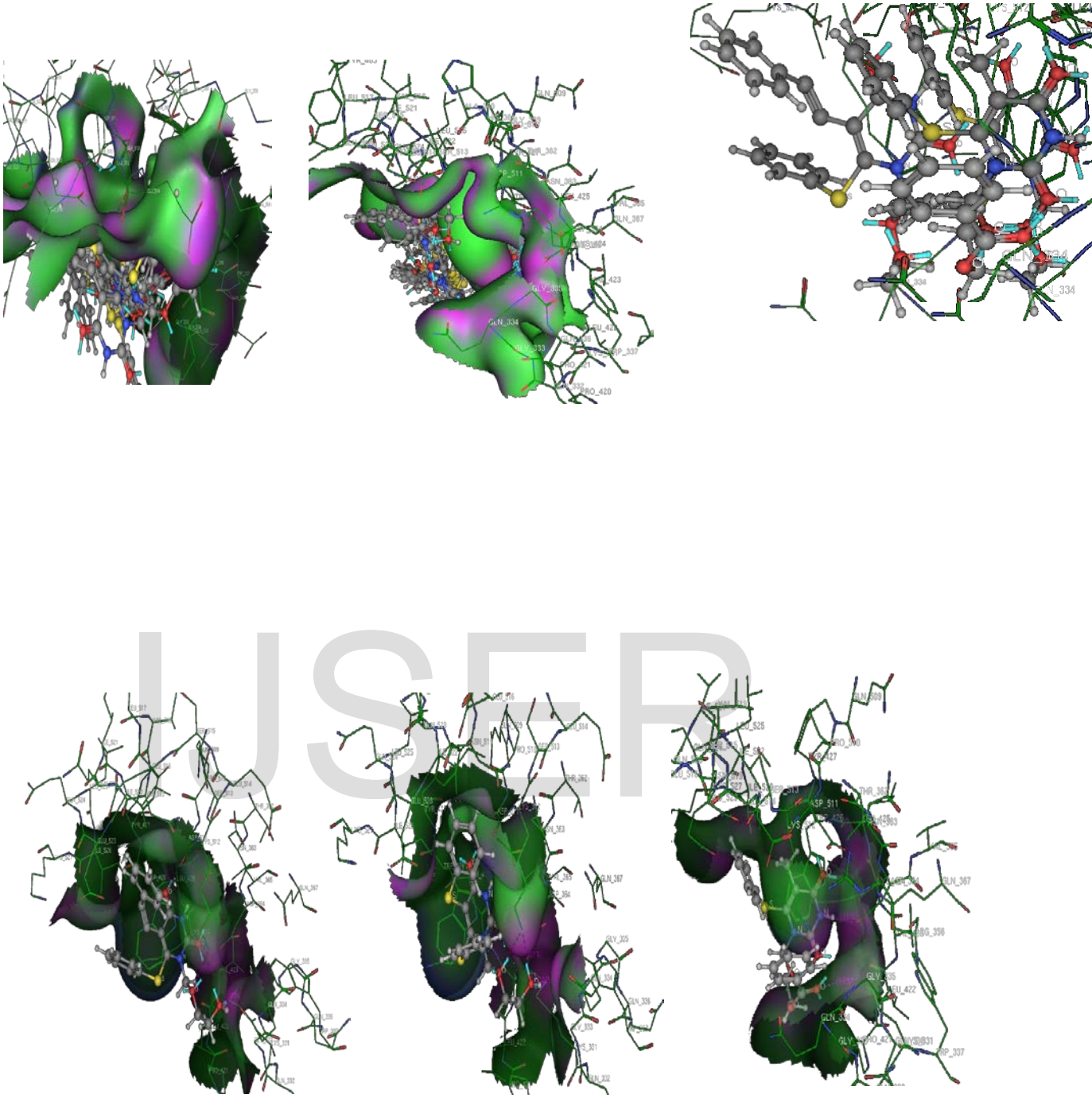
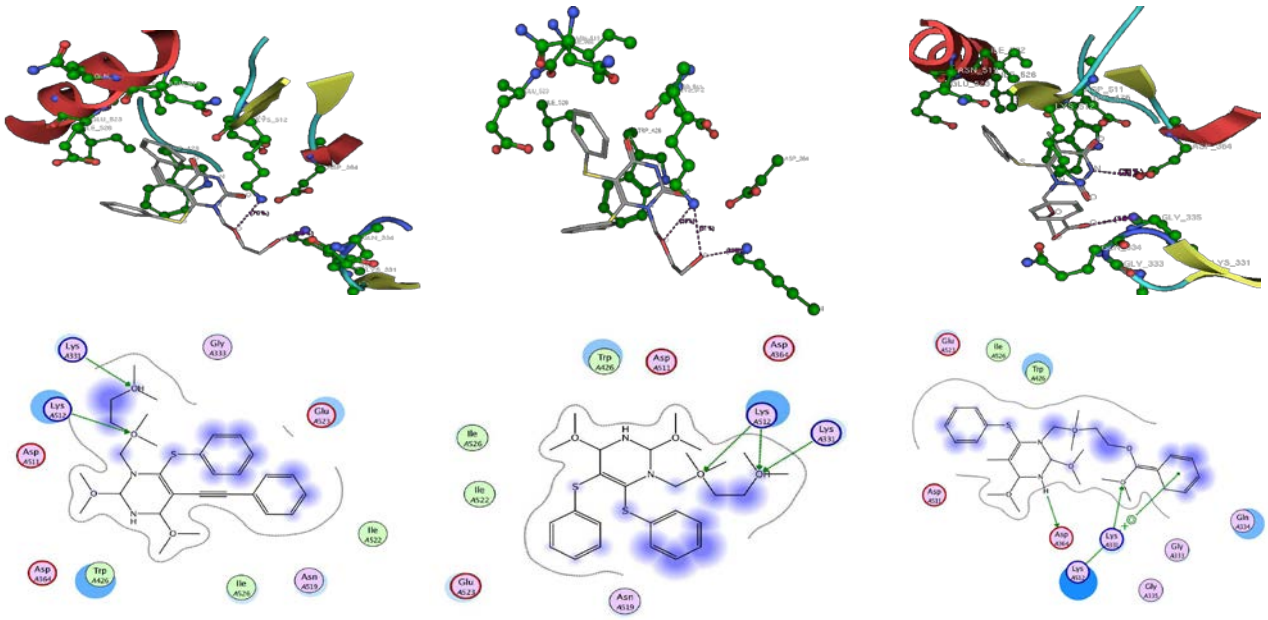
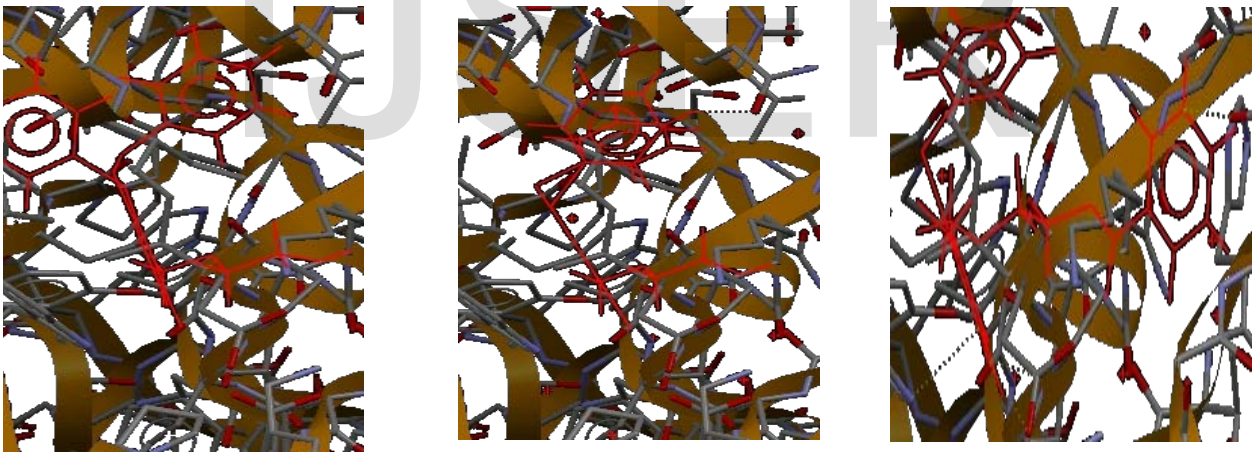


Figure-1: HIV-1 RT receptor protein 3DLK (1st row), Two-dimensional structures of HIV-1 RT inhibitors HEPT H_{97}, H_{95} and H_{44} (2nd row), 10 bioactive conformations of H_{97}, H_{95} and H_{44} (3rd row), docking of bioactive conformations of each inhibitor within 3DLK pocket (4th row), potent conformations of each inhibitors having minimum potential energy (5th row) and best fit docked conformations of each inhibitors with 3DLK (6th row).





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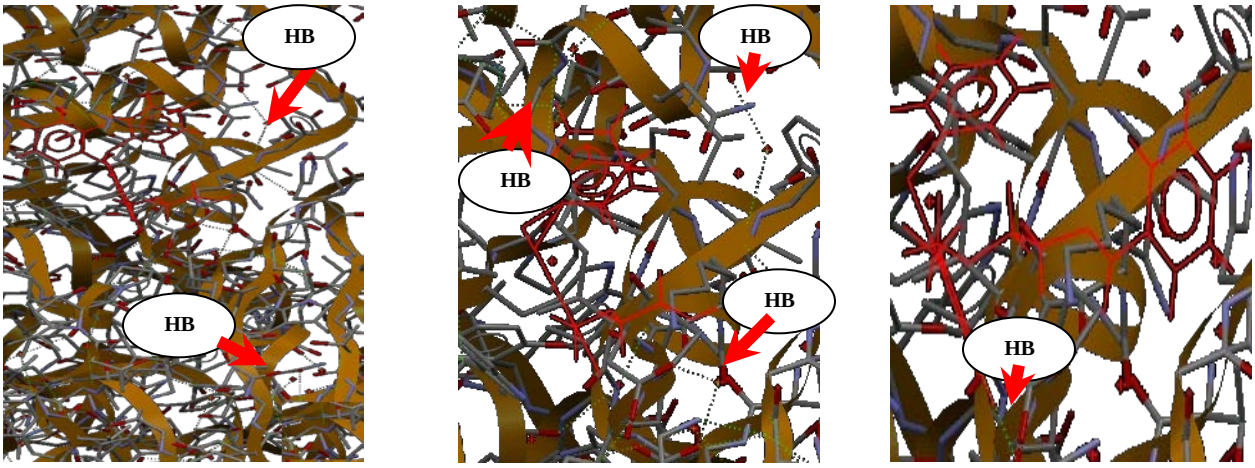

Figure-2: Interactions found between [H_{97}_LYS_{A512}_LYS_{A331}], [H_{95}_ LYS_{A512}_LYS_{A331}] and [H_{44}_ LYS_{A512}_LYS_{A331}_ ASP_{A364}] respectively (1st and 2nd rows), view of short contacts (3rd row) and hydrogen binding found in H_{97}, H_{95} and H_{44} (4th row).

3 RESULTS

TABLE-1: MOLECULAR DOCKING OF HIV-1 RT HEPT WITH 3DLK

1ST REPEAT OF DOCK CYCLE

INHIBITORS	FITNESS	S (HB_EXT)	S (VDW_EXT)	S (INT)
H95	59.61	12.01	37.57	-4.06
H97	59.45	12.03	38.73	-5.83
H72	54.65	3.50	38.66	-2.00

2ND REPEAT OF DOCK CYCLE

INHIBITORS	FITNESS	S (HB_EXT)	S (VDW_EXT)	S (INT)
H97	60.26	12.00	38.77	-5.05
H95	58.09	12.00	36.84	-4.57
H100	56.73	11.98	37.09	-6.24

3 RD REPEAT OF DOCK CYCLE

INHIBITORS	FITNESS	S (HB_EXT)	S (VDW_EXT)	S (INT)
H97	61.63	10.02	40.32	-3.83
H95	60.42	12.00	38.32	-4.27
H44	56.87	10.05	43.49	-12.99

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4 DISCUSSIONS AND CONCLUSION

The molecular docking is termed as molecular associations between bioactive macro-molecules (receptor proteins and micro-molecules (ligand) that essential for signal transduction pathways. These type of experiments based on lock-and-key, induced-fit model and binding affinity mechanisms.

In this study, the attempts have been made for direct receptor based approach by flexible molecular docking on one hundred twenty 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio) (thymine)] (HEPT) inhibitors of HIV-1 non-nucleoside reverse transcriptase (HIV-1 NNRTI) with 3DLK (E.C. 2.7.7.49) protein by using GOLD and MOE. The main object for conducting this research was obtained bioactive conformations of potent anti-AIDS or anti-HIV drugs with desired pharmacological properties for combating life threaten HIV infection, AIDS and AIDS related diseases. It is also helpful to analyze binding interaction between HIV-1 RT inhibitors and receptor.

After two repeats of dock cycles, bioactive conformations were selected on the base of score, root mean square deviation (RMSD), potential energies and close contacts estimated by hydrogen bonding stabilization energy, van der waals internal energy for conformations and interaction energy of bio-molecular complex. The H-97, H-95 and H-44 were found best fit within favorable regions of 3DLK pocket. The H-97 was scored 61.63 with 10.02 (hydrogen binding energy), 40.32, -3.83, (van der Waals external/internal energies) while H-95 was best fitted with 60.42 along estimated hydrogen binding energy and van der Waals energies 12.00, 38.32 and -4.27 respectively. On the other hand, H-44 was ranked at 56.87, with 10.05; hydrogen and 43.49/-12.99 van der Waals energies respectively (table-1).

It is observed that the overall 3DLK (HIV-1 reverse transcriptase receptor) has important amino profile such as GLN-524, LYS-527, ILE-521, GLN-520, LEU-517, ILE,526, GLU-523, ILE-522, VAL-518, GLU-516, ASN-519, TYR-427, SER-515, TRP-426, ASN-509, PRO-510, ASP-511, ASP-364, SER-513, GLU-514, LYS-512, ILE-425, THR-362, LYS-424, ASN-363, VAL-365, ASP-314, VAL-423, LEU-422, GLY-333, GLN-334, PRO-421, GLY-333, LYS-331, GLN-332, TRP-337. But ASP-364 GLY-335, LYS-A331, LYS-A512, ASP-511, TRP-426, TRP-511, ILE-522, ILE-526, GLU-523, GLN-334, GLY-333 and ASN-519 amino acids were found as part of active site within 5Å distance for forming molecular interactions between ligand and protein. The inhibitor H-97 has two strong bond pairs N-O (38%), N-O (84%) with LYSA512, short contacts and hydrogen binding while H-95, has also hydrogen bonding, short contacts and bond pairs O-O (11%), N-O (50%) and N-O (60%) with LYS331 AND lys-512 respectively. The H-44 has interactions N-O (18%), N-O (38%) with GLY-335 and ASP-364 including short contacts as well as hydrogen bindings, (figure-2). Further more, the amino residues especially, LYS-A331, LYS-A512 were found in hydrophobic contacts and salt bridges formation for stabilize the protein structure (figure-1 and figure-2)..

It is concluded that H-97, H-95 and H-44 are highly potent HIV-1 non-nucleoside reverse transcriptase (HIV-1 NNRTI) inhibitors within derived low energy conformational regions of HIV-1 RT receptor (3DLK). They would possibly block reverse transcription by interacting with allosteric pocket of 3DLK or halt the DNA synthesis (single stranded RNA into double stranded DNA and form double helix DNA when RNA has reverse transcribed into a single strand complementary DNA (cDNA) by obstructing the moment of domains of HIV-1 reverse transcriptase to stop HIV-1 for infecting host cell.

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