Bioactive Anti-HIV-1 Reverse Transcriptase (RT) analogues for the treatment of Retroviral Infections, Sexually Transmitted Diseases (STD) and Acquired Immunodeficiency Syndrome (AIDS)

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Abstract
Molecular docking is a modern, fast, cost effective drug design technique that work like induced fit or like lock & key models, simulate molecular recognition, bind medicinal substance to target receptors then block disease causing factors without affecting drug anti-targets to achieve potent drug within receptor's catalytic pocket against life threaten clinical disorders. In this Paper, docking cycles were made between 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio) thymine derivates and 2ZD1 protein and obtained potent anti-HIV-1 RT life saving combaters.

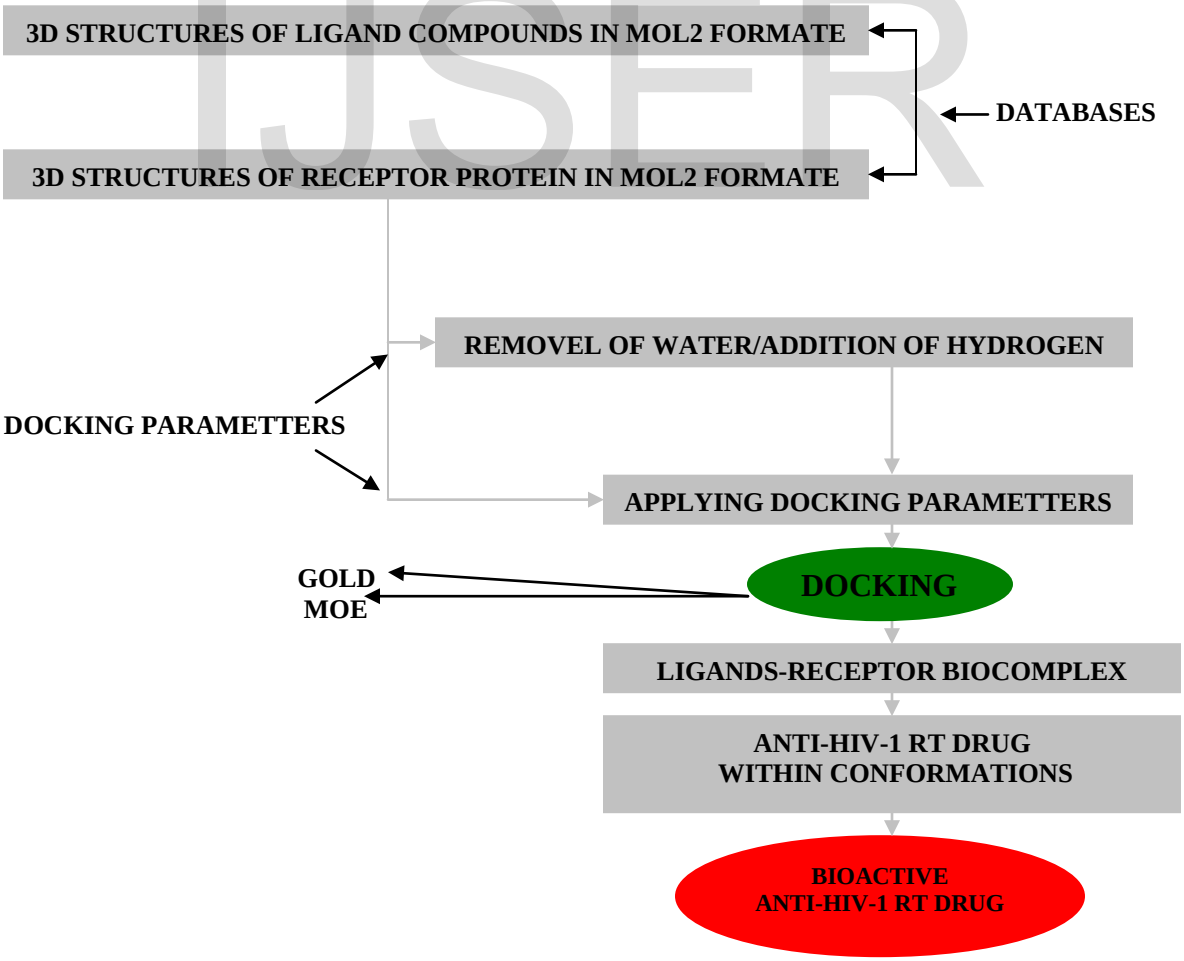
Key Words
Molecular docking, Protein-ligand docking, Acquired immunodeficiency syndrome (AIDS), Human Immunodeficiency Virus (HIV), HIV-1 reverse transcriptase (HIV-1 RT), Inhibitors, Drugs, Receptor proteins, Amino Acids and Active site.

1 INTRODUCTION
The reverse process in which viruses can able to make DNA from RNA is termed as retroviral transcription and viruses are known as retroviruses such as Human immunodeficiency Virus (HIV) [7, 13, 18, 20]. They infect T-helper cells, macrophages, monocytes, B-lymphocytes, microglia, astrocytes, oligodendrocytes, neurones, glycoprotein-120 and cause damage of immune system lead towards retroviral infection and sexually transmitted diseases (STD) like Acquired immunodeficiency syndrome. While AIDS is a severe cluster of multiple retroviral infections that can be symptomatic, a symptomatic, dormant with visible decrees level of CD4 count weak immune system to patient's death[40, 50, 53, 65].

In past, cure against HIV infection or AIDS was very critical but now it has little bit easier after discovery of many antiretroviral drugs [6, 23] or inhibitors by combinational drug design [9, 14, 15, 21, 22, 48, 25, 29, 30 21,] and clinical research. These drugs are given to patients in form of simple, fix, combination, synergistic and regimens doses that known

as antiretroviral therapy (ART). Entitled study was conducted to design potent antiHIV-1 reverse transcriptase (RT) [2, 32] drug like compounds within bioactive conformations[38, 45]. It is also provide depth insight of strong molecular association between drug and receptor, energy profile and target place where drug or inhibitor can block actual mechanism of reverse transcription or disable the virus for infecting host cell. Therefore, one hundred-twenty (1-[(2-hydroxyethoxy) methyl]-6-(phenylthio) thymine) (HEPT) [33, 57] derivates were docked with HIV-1 reverse transcriptase protein 2ZD1 by using GOLD and MOE. These inhibitors can be classify as non-nucleoside reverse transcriptase inhibitor (NNRTI) and able to reduced viral load or halt viral replication by interacting to allosteric pocket of 2DZ1 (E. C. 2.7.7.49). On the other hand, docking [5, 11, 19, 26, 39]. is a process where a drug creates molecular associations [16, 17, 31] with specific receptor for forming bio-molecular complex that may accelerate or block target of interest, make the drug act like agonist or antagonist with in best fit conformations against clinical disorders, [3, 10, 12, 43, 52]. Where about, docking package[51, 64] like GOLD [5, 8, 27, 36, 59, 60, 61] is used for single or cluster docking within catalytic site that can modeled clinically active drug[55, 58, 62]. While, molecular operating environment (MOE) [35, 41, 47, 49, 54] is useful for designing a drug for medicinal use with help of scientific vectors.

2 METHOD



Scheme: Molecular docking by using GOLD and MOE.

3 FIGURES

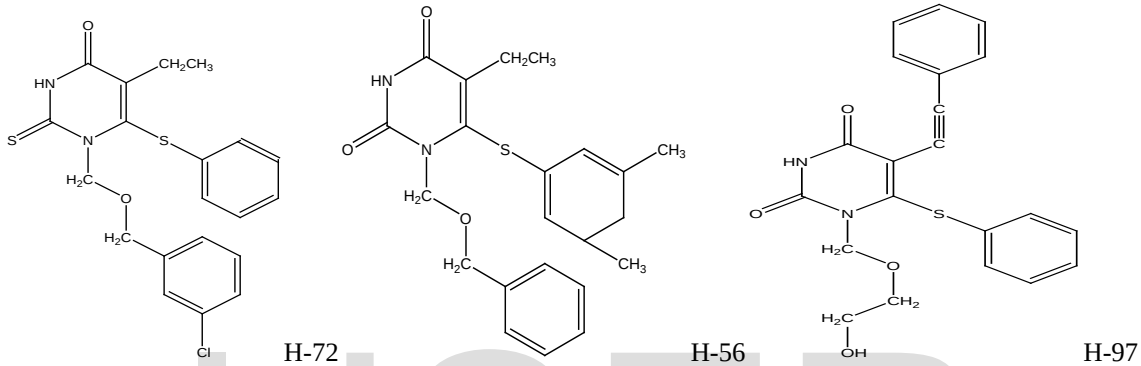


Figure-1: Two-dimensional structures of H-72, H-56 and H-97.

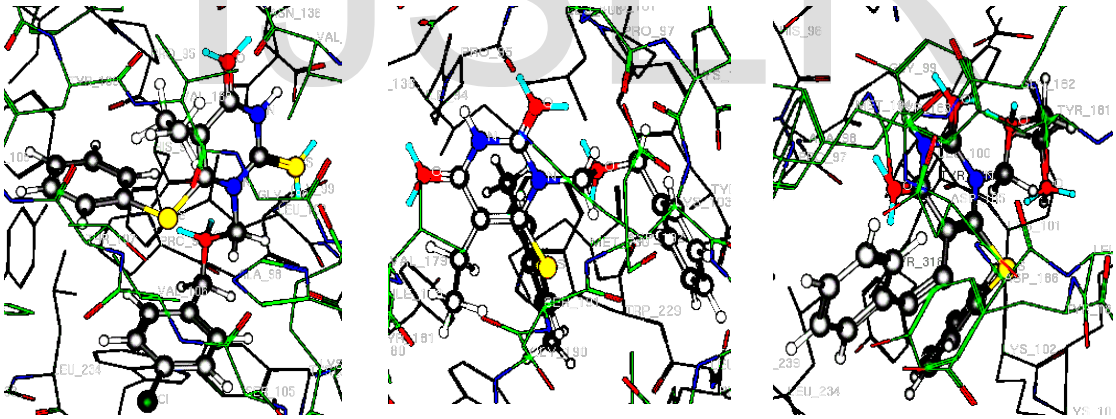


Figure-2: Three-dimensional bioactive conformations of H-72, H-56 and H-97 with 2ZD1protein.

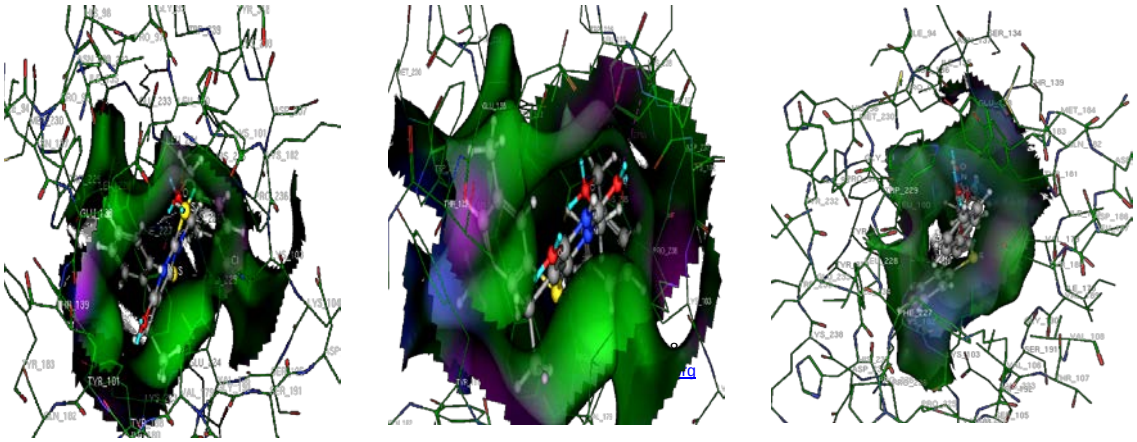


Figure-3: docking of potent conformations of H-72, H-56 and H-97.

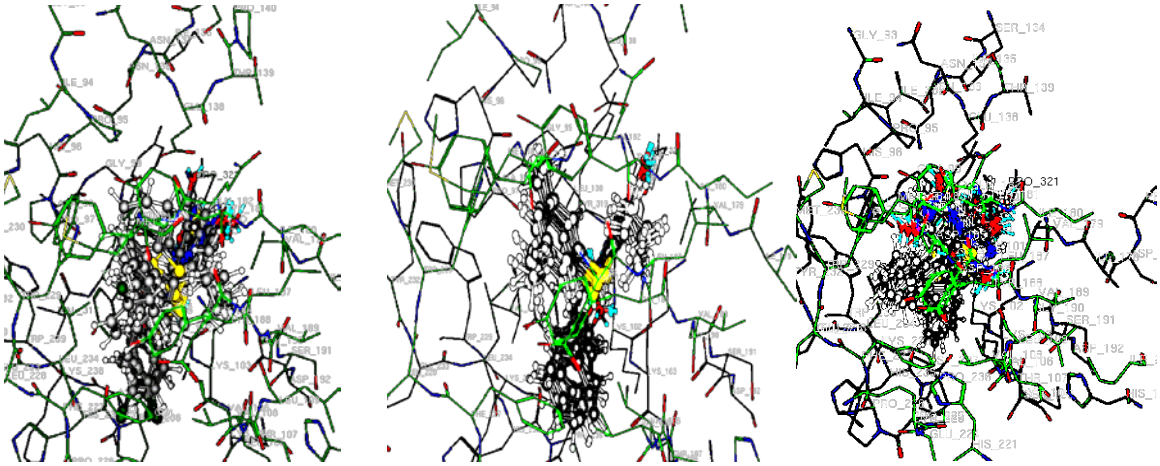


Figure-4: Thirty bioactive lower energy conformations of H-72, H-56 and H-97.

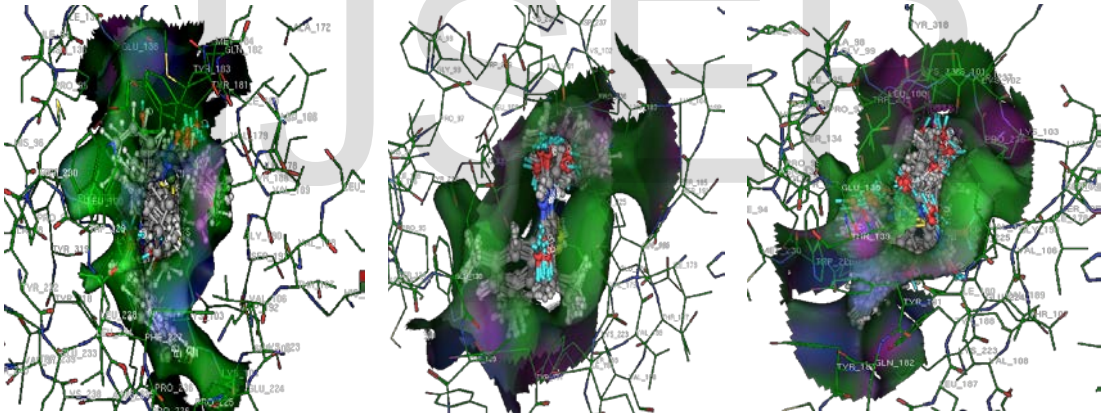


Figure-5: docking of bioactive lower energy conformations of H-72, H-56 and H-97.

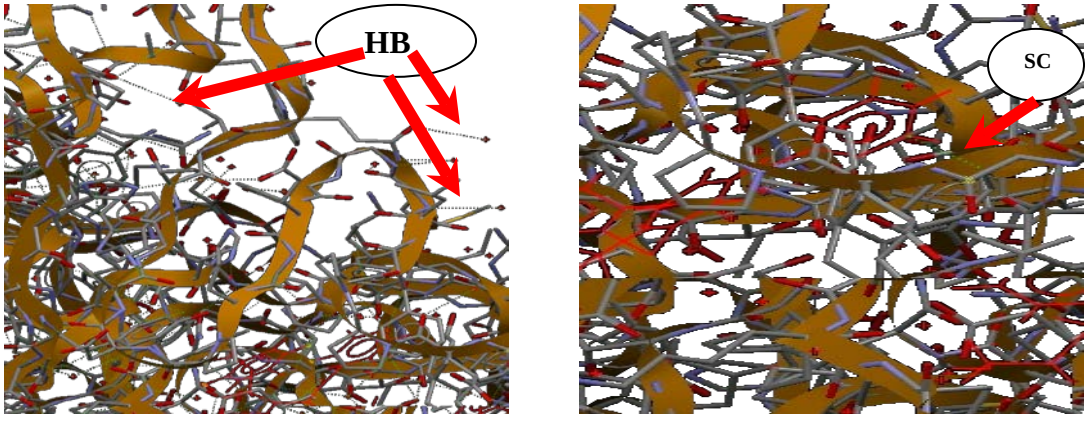


Figure-5: Hydrogen binding found in (H-72, H-56 and H-97) and short contact in H-97,

4 RESULTS

TABLE-A: 1ST REPEAT OF DOCK CYCLE ON HIV-1 RT HEPT INHIBITORS WITH 3DLK

INHIBITORS	FITNESS	S (HB_EXT)	S (VDW_EXT)	S (INT)
H72	83.23	0.97	64.24	-6.06
H56	80.35	1.99	62.55	-7.65
H97	76.90	1.76	57.08	-3.35

TABLE-B: 2ND REPEAT OF DOCK CYCLE ON HIV-1 RT HEPT INHIBITORS WITH 3DLK

INHIBITORS	FITNESS	S (HB_EXT)	S (VDW_EXT)	S (INT)
H72	83.78	1.09	64.58	-6.11
H56	81.15	1.76	63.10	-7.37
H97	76.81	0.42	59.99	-6.10

TABLE-C: 3 RD REPEAT OF DOCK CYCLE ON HIV-1 RT HEPT INHIBITORS WITH 3DLK

INHIBITORS	FITNESS	S (HB_EXT)	S (VDW_EXT)	S (INT)
H72	84.24	1.09	64.92	-6.12
H56	82.00	1.77	64.13	-7.94
H97	75.70	0.72	59.44	-6.75

5 DISCUSSION AND CONCLUSION

In this study, 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio) (thymine)] (HEPT) compounds were docked on HIV-1 reverse transcriptase (RT) protein 2ZD1 by using Gold 3.0., and MOE (figure-1).

2ZD1 protein (E.C. 2.7.7.49) is composed of two polypeptide chains (A and B), belongs to transferase or hydrolase class of enzymes on 1.80Å resolution with unit cell dimensions (a = 163.37Å, b = 73.26Å, c = 110.07Å with $\alpha = 90°$, $\beta = 100.07°$, $\gamma = 90°$). Active site made up with many important amino residues but GLU-138, TYR-183, TYR-181, VAL-179, TYR-188, SER-103, VAL-106, HIS-235, PHE-227, TYR-318, TRP-229, LEU-234, LYS-101, LEU-100 were associated with catalytic pocket and play endeavor role in reverse transcription process, hydrogen bonding, short contacts as well as other molecular interaction within 5Å distance. The inhibitors H-72, H56 and H-97 were found best fit with fully proton acceptors LYS-$A_{238,}$ LYS-$_{A331}$, LYS-$_{A512}$ within catalytic site that promote ionic environment for stabilizing protein.

The H-72 was scored 84.24 with 1.09 (hydrogen bonding energy), 64.92, -6.12, (van der waals external/internal energies) while H-56 was best fitted with 82.00 with computed hydrogen binding energy and van der Waals energies 1.77, 64.13, and -7.94 respectively.

On the other hand, the H-97 was ranked at 75.70 with 0.72 hydrogen and 59.44/-6.75 (Van der Waals energies).
These docked conformations were selected on the bases of score (sum of hydrogen bonding stabilization energy, van der Waals internal energy of conformations, interaction energy of bio-molecular complex) root mean square deviation (RMSD), potential energies and close contacts.

It is concluded that H-72, H-56 and H-97 inhibitors within derived conformations are more potent as compared to rest of HEPT inhibitors as per above docking interpretation. They would possibly inhibit reverse transcription as bioactive anti-HIV-RT compounds within lower energy conformation.

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