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Research Article

Virtual Screening for Novel HIV-Reverse Transcriptase Inhibitors

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Abstract

HIV–1 (human immunodeficiency virus type–1) is the disease causing agent for AIDS. It is pathogenic retrovirus which joined in a long polypeptide chain when viral RNA is translated into a polypeptide sequence. It contains different proteins like reverse transcriptase, protease, integrase, etc. These proteins have to be altered from polypeptide chain before these enzymes become to start function. Reverse transcriptase is inhibited by. We applied existing system by virtual screening analysis of HIV-RT from PDB database versus chemical compounds from ZINC database using "Autodockvina" and "cornia sketch tool". Different hypothetical ligands were deliberate on cornia sketch tool and their structures were docked with (HIV-RT) PDB file. The structure with best recording was selected and the database of zinc was separated for similar structures and consequences in 18 hits.

Keywords: HIV, reverse transcriptase, protease, virtual screening, RMSD, Zinc data base, Autodock grid, Autodockvina, docking

INTRODUCTION

Human immunodeficiency virus cause acquired immunodeficiency syndrome (AIDS). It is a situation in which the immune system instigates to fail in human, it leads, to life-threatening infections (Kandathil *et al.*, 2009). Acquired immune deficiency syndrome (AIDS) is a disease that inflict destruction in the world. Reverse transcriptase, protease and integrase are coded by the gag and gag–pol genes of HIV that shows a significant role in the repetition cycle of virus. Viral reverse transcriptase (RT) cause catalyzation in the development of proviral DNA from viral RNA. It is key stage in viral replication. Two types of HIV RT inhibitors are discovered. One is nucleoside analoguesnevapin is an example of nonnucleoside RT inhibitors. Development of viral resistance associated with mutations restrict the therapeutic efficacy of the drug.

HIV is about 120 nm in diameter (Blankson *et al.*, 2002) and consists of two copies of positive single- stranded RNA that codes for the virus. Single- stranded RNA is strongly bound to nucleocapsid proteins, p7 and enzymes desired for the progress of the virion such as reverse transcriptase, proteases, ribonuclease and integrase *(Finzi and Siliciano, 1998)*. Viral protein p17 environ capsid ensuring the integrity of the virion particle. It is surrounded by the viral envelope which consist of two layers of fatty molecules called phospholipids.

MATERIALS AND METHODS

Steps in making 1vrt.pdb file ready

For docking we need protein and ligand. Structure of reverse transcriptase was downloaded from www.rcsb.org 1VRT.pdb (Figure 1). There is ligand attach with it.

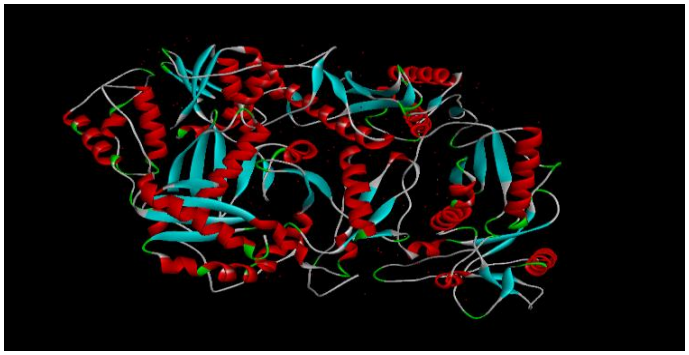

Figure 1: Molecule of enzyme 1VRT downloaded from protein database.

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Removed the already present ligand with the help of software "Discovery studio client" After the removal of ligand figure 2.

Ligand formation and search.

one bound ligand (drug Nivarapine) like nivarapine. Other drugs not have noble structure. Complete structure was searched in zinc database.

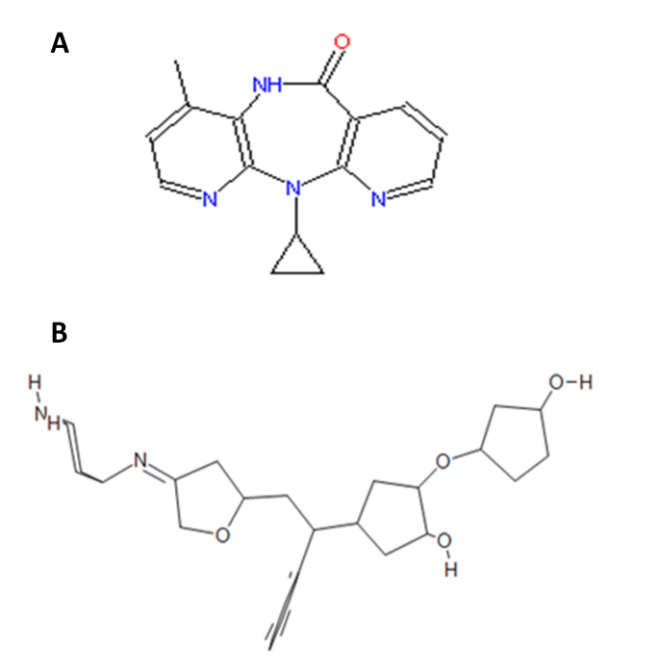

Figure 2: **(A)** Nivarapine Structure and complete structure search in ZINC database. **(B)** pdbqt after that name of that ligand was given into configuration

A suitable ligand was drawn on the cornia sketcher. Its pdb file was downloaded and changed.

Auto dock Vina was used to dock that hypothetical structure with the enzyme the results were better than the drug Nevirapin 7.3Kcal/mol. The interaction between the hypothetical compounds with affinity value -8.3Kcal/mol with enzyme is shown in figure 2. This represents high interaction between the hypothetical structure and enzyme. So we can use compounds with the similar structures to dock with 1VRT molecule.

The structure of hypothetical compound was drawn by using tool in zinc database. No like structures available in zinc database; hence, we relax the criteria by 70%. We find 18 best hits. These compounds were docked with the enzyme 1VRT. All of these compounds were downloaded in SDF 3d structure and then converted into PDB file with the help of discovery studio. Then these PDB files were converted into PDBQT file type. This file type is necessary for docking. No. of torsions are set in the auto dock. These files were used by Auto dock vina to perform docking. In docking we get 9 different orientations of a ligand. Best orientation is with the RMSD value 00 we have shown all the orientations possible in one image and lingand of best value in second image.

1VRT was copied from Protein Data Bank.

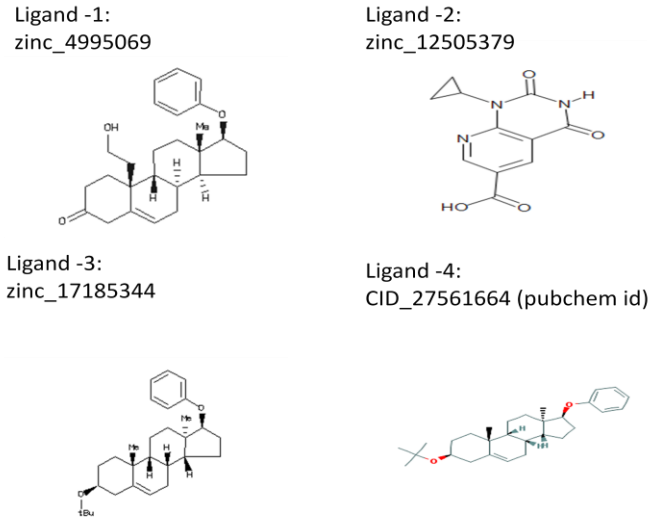

Figure 3: Ligand 1, 2, 3, 4. Zinc and CID

RESULTS AND DISSCUSIONS

We design a hypothetical compound which resulted in 36 ligands. Binding properties of

each pose with the receptor was assessed based on docked energies. The technique used in the study gives us 9 different orientation of ligands. After screening the best compounds we selected.

Table 1: Show energies of Ligands and Navaprine for different orientations.

Compound (I.D)	1) Kcl/mol	2) Kcl/mol	3) Kcl/mol	4) Kcl/mol	5) Kcl/mol	6) Kcl/mol	7) Kcl/mol	8) Kcl/mol	9) Kcl/mol
Navaprine	-7.3	-7.1	-6.8	-6.7	-6.7	-6.5	-6.5	-6.4	-6.3
Hypotheticalcompound	-8.3	-8.2	-8.1	-8.0	-8.0	-8.0	-7.9	-7.7	-7.7
zinc_4995069	-9.7	-8.6	-8.6	-8.5	-8.2	-7.9	-7.9	-7.9	-7.8
zinc_12505379	-8.9	-8.7	-8.6	-8.6	-8.5	-8.2	-8.1	-8.0	-7.9
zinc_17185344	-8.9	-8.8	-8.6	-8.5	-8.5	-8.2	-7.9	-7.9	-7.8
CID_27561664 (pub-chem id)	-9.1	-9.0	-8.9	-8.9	-8.8	-8.3	-8.3	-8.1	-8.1

As shown in Table 1, it became obvious that four best ligand conformers with improved binding compatibilities than 1VRT bound ligand.

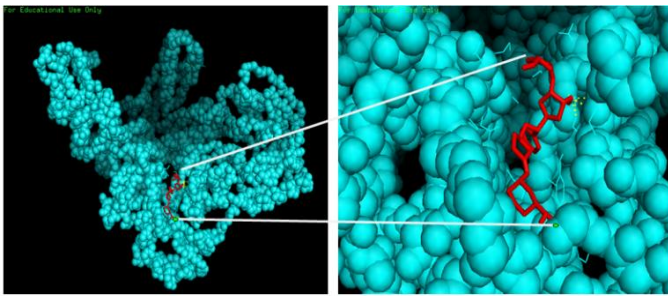

Figure 4: Ligand with enzyme molecule having energy -8.3kcl/mol.

It shows enzyme's binding pocket and polar connections between enzymes and ligand. We use the structure of this molecule and found similar structure in zinc data base.

Ligand-1 zinc_4995069

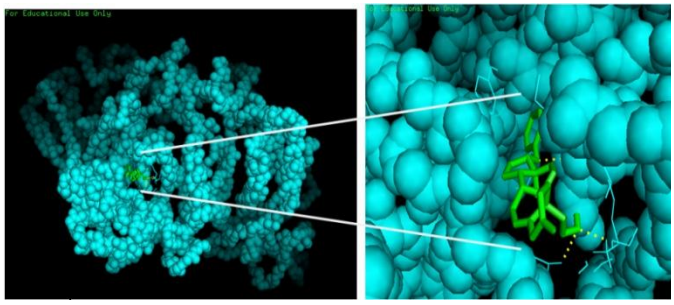

Figure 5: Ligand with highest binding affinity 9.7kcal/mol.

Paymol software was used to find out the orientation and binding pocket of the enzyme molecule. It is shown that there are more polar bond of this ligand with enzyme residues. Its interaction with enzyme is stronger and larger size show the binding pocket so clear.

Ligand-2 zinc_17185344

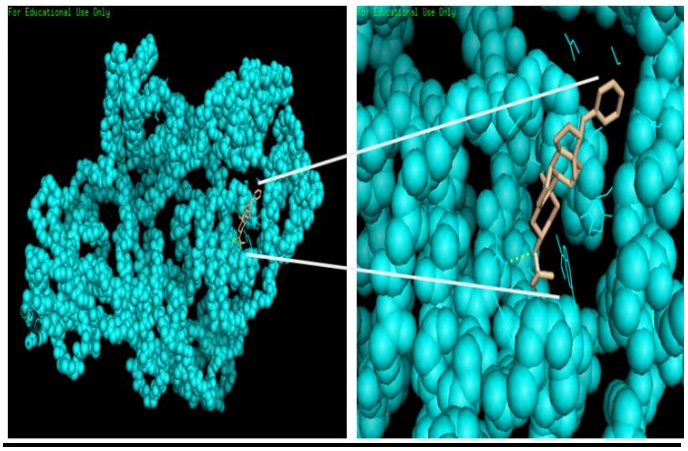

Figure 6: Ligand with binding affinity 8.9kcal/mol.

Pay-mol software was used to find out the orientation and binding pocket of the enzyme molecule. It is shown that there are more polar bonds of this ligand with enzyme residues then navaprine. Its interaction with enzyme and binding pocket are shown clear in the larger figure.

Ligand-3 zinc_12505379

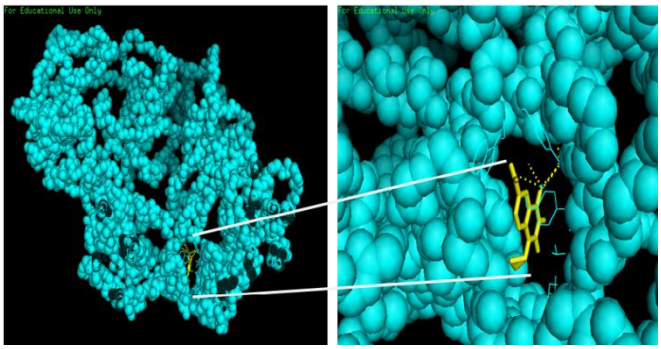

Figure 7: Ligand with binding affinity 8.9kcal/mol.

Pay-mol software was used to find out the orientation and binding pocket of the enzyme molecule. It is shown that there are more polar bonds of this ligand with enzyme residues then navaprine. Its interaction with enzyme and binding pocket are shown clear in the larger figure.

Ligand-4 CID_27561664(pub-chem-id)

Pay-mol software was used to find out the orientation and binding pocket of the enzyme molecule. It is shown that there are more polar bonds of this ligand with enzyme residues then navaprine. Its interaction with enzyme and binding pocket are shown clear in the larger figure.

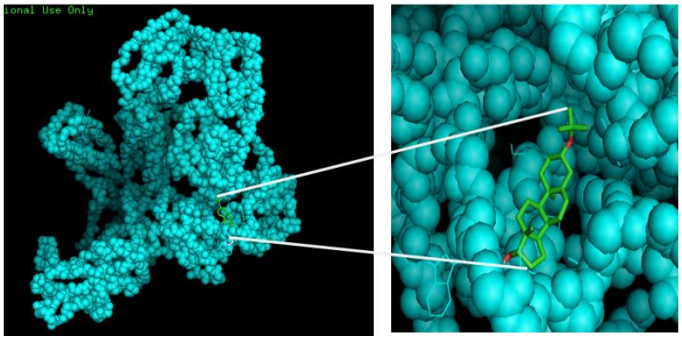

Figure 8: Ligand with binding affinity 9.1kcal/mol.

We use chem.-sketcher software to find the ADMET properties of these compounds table 2.0 represent them

CONCLUSION

This study show that through docking ligand best molecules are choose. IVRT results in 36 molecules out of 4.6 million. By using different screening methods four best molecules are selected by zinc_4995069, CID_27561664 (pub-chemid) and zinc_12505379 zinc_17185344 with auto-dock scores of -9.7, -9.1, -8.9 and -8.9 kcal/mol respectively.

Table 2: Admet properties of the given compound.

Structure Name	MlogP	S+log	S+logD	Rule of 5	Rule of 5 code	Mwt	M-No	T-PSA	HBDH
CID_27561664 (pub-chem id	5.879	8.34	8.34	1.000	LP	422.655	2.000	18.46	0.000
zinc_4995069	4.362	4.646	4.646	1.000	LP	394.558	3.000	46.53	1.000
zinc_12505379	-0.682	0.22	-1.436	0.000		247.2	7.000	105.1	2.000
zinc_17185344	5.879	8.34	8.34	1.000	LP	422.7	2.000	18.46	0.000

Absorption, metabolism, distribution, toxicity, excretion: A set of test classes used together in drug discovery to provide awareness into how a pharmaceutical drug interacts with the body as a whole.

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