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Screening ZINC database for novel HIV-1 reverse transcriptase Inhibitors

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ABSTRACT

Human immunodeficiency virus (HIV) is a retrovirus that causes acquired immunodeficiency syndrome. HIV-1 reverse transcriptase (RT) is a multifunctional enzyme that copies the RNA genome of HIV-1 into DNA. The dipyridodiazepinone Nevirapine is a potent and highly specific inhibitor of the reverse transcriptase (RT) from human immunodeficiency virus type 1 (HIV-1). It is a member of an important class of non-nucleoside drugs. In this paper, we report virtual screening analysis of HIV-RT from PDB database versus chemical compounds from ZINC database using eHiTS software. Using molecular constraint search, 884 ligands were extracted and docking analysis resulted in 59 best hits. Based on binding compatibilities with receptor, top three molecules (ZINC04923148, ZINC05442451 and ZINC04923002) were reported as possible novel HIV-RT inhibitors.

Keywords: HIV reverse transcriptase, virtual screening, ZINC database, ehits, docking

INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that causes acquired immunodeficiency syndrome (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections [1]. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells [2].

HIV is different in structure from other retroviruses [3]. It is about 120 nm in diameter and roughly spherical. It is composed of two copies of positive single- stranded RNA that codes for the virus's nine genes enclosed by a conical capsid composed of 2,000 copies of the viral protein p24. The single- stranded RNA is tightly bound to nucleocapsid proteins, p7 and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonuclease and integrase [4]. A matrix composed of the viral protein p17 surrounds the capsid ensuring the integrity of the virion particle. This is, in turn, surrounded by the viral envelope which is composed of two layers of fatty molecules called phospholipids taken from the membrane of a human cell when a newly formed virus particle buds from the cell [5].

HIV-1 reverse transcriptase (RT) is a multifunctional enzyme that copies the RNA genome of HIV-1 into DNA. It is a heterodimer composed of a 66 kDa (p66) and a 51 kDa (p51) subunit. HIV-1 RT is a crucial target for structure-based drug design [6], and potent inhibitors have been identified, whose efficacy, however, is limited by drug resistance. The amino acid residues involved in drug resistance of HIV-1 reverse transcriptase are Leu100, Val106, Val108, Val179, Tyr181, Tyr188, Lys103, Gly190, Met230 and Pro236 [7]

The dipyridodiazepinone Nevirapine is a potent and highly specific inhibitor of the reverse transcriptase (RT) from human immunodeficiency virus type 1 (HIV-1). It is a member of an important class of nonnucleoside drugs [8] that appear to share part or the entire same binding site on the enzyme but are susceptible to a variety of spontaneous drug-resistance mutations [9].

In this study, a virtual screening routine was reported by utilizing 1VRT from protein data bank and screening based on docking ZINC database ligands for effective HIV-RT inhibitor.

MATERIALS AND METHODS

The 3-dimensional coordinates of X-ray crystallographic structure of HIV reverse transcriptase in complex with nevirapine (PDB ID: 1VRT) was downloaded from Protein Data Bank and used as receptor structure for virtual screening program. Chemical library, ZINC database and the docking program eHiTS (electronic High Throughput Screening) was employed in the study.

ZINC database has over 4.6 million compounds in ready-to-dock formats. The database was screened for compounds with either similar geometrical features or Lipinski compliant [10]. The physico-chemical properties such as log P value, H-bond donors, H-bond acceptors, molecular weight and rotational bonds, of nevirapine ligand were calculated using Tsar software (www.accelrys.com).

eHiTS (http://www.simbiosys.ca) has a novel flexible ligand docking method and generates poses that avoid severe steric clashes between receptor and ligand. The algorithm is exhaustive on the conformations and the conformers are compatible with the steric and chemistry constraints.

RESULTS AND DISCUSSION

Before screening ZINC database, the ehits docking protocol was validated. 1VRT protein bound ligand nevirapine was docked into the binding pocket and the RMSD (Root Mean Square Deviation) of the docked pose was 0.55 A° (Figure 1) with co-crystallized ligand, indicating that the parameters for docking simulation are good in reproducing the X-ray crystal structure.

A structure based search using structural features that are similar to nevirapine resulted in no hits. Hence, a molecular constraint search was employed using physico-chemical properties of nevirapine which resulted in 884 ligands. All these ligands are found to be Lipinski compliant. All compounds are docked and the binding compatibility of each pose with the receptor was evaluated based on docked energies. The technique used in the study identified diverse geometrical ligands but specific in displaying binding compatibilities with the receptor active site region. From the screening analysis of 884 ligands, a total of 59 molecules resulted in high dock scores (>-6.58 to -8.179 kcal.mol) than the original nevirapine molecule (-6.5818 kcal/mol). The ZINC id's along with binding energy scores for top three molecules are given in Table 1.

Table 1. The best three ZINC hits

S. No.	ZINC ID	e-hits score (kcal/mol)
1	1VRT bound nevirapine	-6.582
2	ZINC04923148	-8.179
3	ZINC05442451	-7.886
4	ZINC04923002	-7.424

Figure 1 shows the image of original ligand bound within active site region of 1VRT protein with a conformer representing the RMSD value of 0.55 A^{o} with e-hits score of -6.5818 kcal/mol. Therefore, when a screening analysis is performed against 1VRT protein, any such molecule which binds to 1VRT with a score better than -6.5818 kcal/mol is of prime interest in this screening schedule. Therefore, from the analysis, as given in Table 2, it became evident that there existed about three best ligand conformers with netter binding compatibilities than 1VRT bound ligand. The number of interacting residues for nevirapine, ZINC04923148, ZINC05442451, and ZINC04923002 molecules are given below.

Table 2. Number of H-bond interactions between 1VRT and top poses of screening outcome.

S. No	ZINC ID	SCORE (kcal/mol)	No. of INTERACTIONS	INTERACTING RESIDUES
1	NEVIRAPINE	-6.582	16	CB TYR-181, CB TYR-181 CD1 LEU-100, CD1 LEU-100 CD1 LEU-100, CG LEU-234 CG2 VAL-106, CG2 VAL-106 CG2 VAL-106, CD1 LEU-100 CD1 LEU-100, CD1 LEU-100 CD1 LEU-100, CZ3 TRP-229 CB TYR-181, CG2 VAL-106 CG1 VAL-179, CD2 LEU-100 CD2 LEU-100, CD1 LEU-100
2	ZINC04923148	-8.179	19	CD1 LEU-100, CD1 LEU-100 CB LEU-100, CD1 LEU-100 CD1 LEU-100, CD1 LEU-100 CD1 LEU-100, CB TYR-188 CG LEU-234, CG LEU-234 CD1 LEU-100, CD1 LEU-100 CG TYR-181, CZ TYR-188 N LYS-101
3	ZINC05442451	-7.886	19	CA PRO-236, CD1 LEU-100 CD1 LEU-100, CD1 LEU-100 CG1 VAL-106, CG1 VAL-106 CG2 VAL-106, CG2 VAL-106 CD1 LEU-100, CD1 LEU-100

4	ZINC04923002	-7.424	20	CD1 LEU-100, CD1 LEU-100 CD1 LEU-100, CD1 LEU-100 CG TYR-181, CE2 TYR-181 CD1 LEU-100, CD1 LEU-100 OH TYR-318 CG PRO-95, CD1 LEU-100 CD1 LEU-100, CD1 LEU-100 CD1 LEU-100, CD1 LEU-100 CD1 LEU-100, CZ TYR-188 CD1 LEU-100, CD1 LEU-100 CD1 LEU-100, CB LEU-100 CB LEU-100, CD2 LEU-100 CD2 LEU-100, CD2 LEU-100 CB LEU-100, CD LYS-101 CG2 VAL-106, N LYS-101

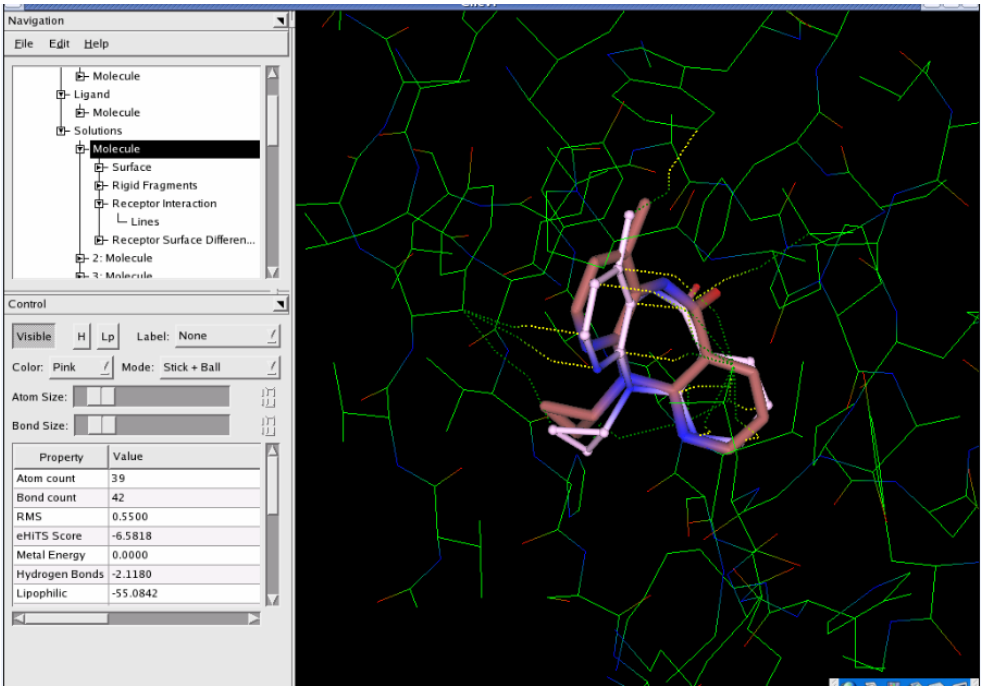

Figure 1. 1VRT bound nevirapine (-6.5818 kcal/mol) with active site residue interactions displaying protein structure in background and RMSD 0.55 A°.

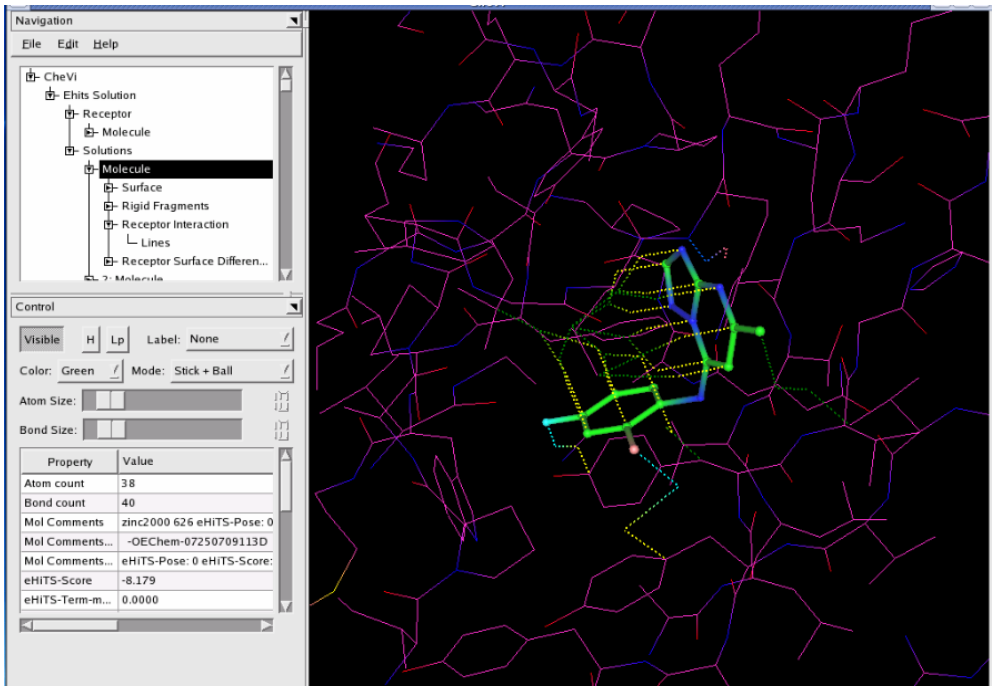

Figure 2. 1VRT with docked pose of ZINC04923148 showing e-hits score of -8.179 kcal/mol.

ZINC04923148 represented better orientation (Figure 2, -8.179 kcal/mol) with possible H-bond interactions being 19 and the Lipinski data are: H-bond donors 1, H-bond acceptors 5, molecular weight 277.69, logp 3.17 and number of rotatable bonds 2, respectively. From the table it is also evident that the molecule exhibited more number of interactions than the original ligand. In order to study the probable reason behind difference in number of interactions, the residue wise atomic interactions for each molecule was evaluated. From the interaction list, individual interactions between atomic coordinates of 1VRT active site residues and ZINC ligand displayed the high score for 18th interaction showing TYR-188 residue CZ atom interaction with ligand. This was mainly due to the Lone electron pair of a halogen atom of ligand and Pi electron of an aromatic ring of 1VRT. The best interaction from 19 interacting atoms between receptor and ligand of ZINC04923148 was given below.

Receptor SPT	[16] Pi electron of an aromatic ring
Ligand SPT	[21] Lone electron pair of a halogen atom (F,Cl,I)
Dihedral angle	162.20
Distance	3.9245
Score	-2.5779
Receptor atom	Index:206 Residue: CZ TYR-188 Type:C
Ligand atom	Index:18 Type:F

ZINC05442451 ligand (Figure 3, -7.886 kcal/mol) with about 19 interactions and the Lipinski data are: H-bond donors 1, H-bond acceptor 6 and molecular weight 278.678, logp 2.63 and number of rotatable bonds 2, respectively. Individual interactions between atomic coordinates of 1VRT active site residues and ZINC ligand displayed the high score for 15th interaction showing TYR-181 residue CG atom interaction with ligand. This was mainly due to the Lone electron pair of a halogen atom of ligand and Pi electron of an aromatic ring of 1VRT. The best interaction from 19 interacting atoms between receptor and ligand of ZINC05442451 was:

Receptor SPT	[16] Pi electron of an aromatic ring
Ligand SPT	[21] Lone electron pair of a halogen atom (F,Cl,I)
Dihedral angle	166.51
Distance	3.2061
Score	-1.7645
Receptor atom	Index:154 Residue: CG TYR-181 Type:C
Ligand atom	Index:15 Type:Cl

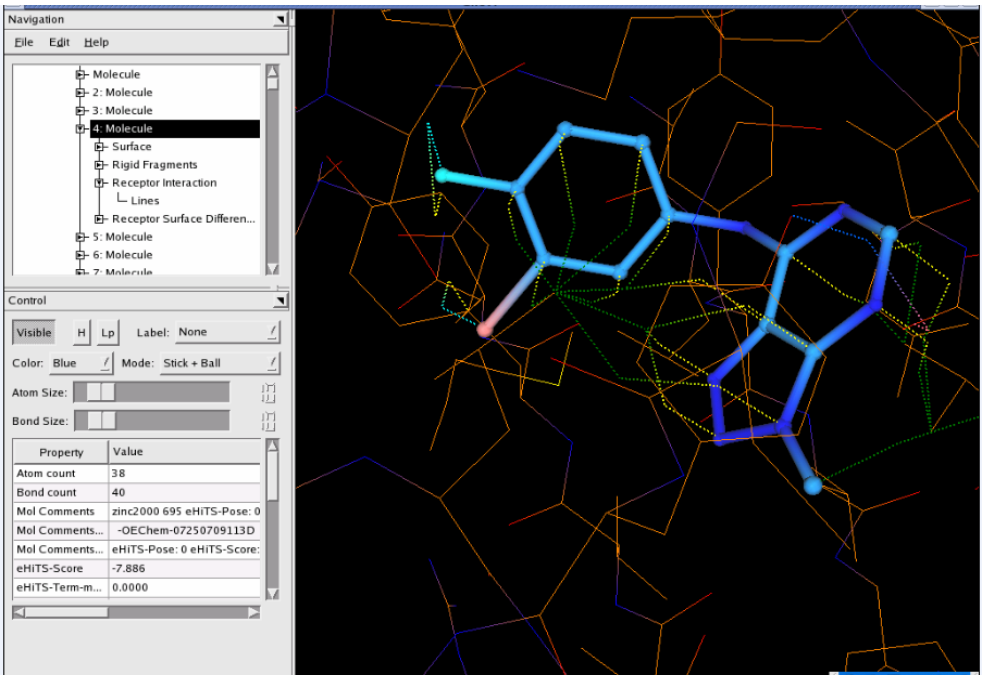

Figure 3. 1VRT vs ZINC05442451 showing e-hits score of -7.886 kcal/mol.

ZINC04923002 ligand (Figure 4, -7.424 kcal/mol) with about 20 interactions and the Lipinski data are: H-bond donors 1, H-bond acceptor 5 and molecular weight 271.299, logp 3.02 and number of rotatable bonds 2, respectively. From the interaction list, 20th interaction showing LYS-101 residue N atom interaction with ligand was found to be the best, mainly due to the strong (primary) hydrogen bond acceptor lone pair atom of ligand and Strong (primary) hydrogen bond donor H (polar-atom-H) of 1VRT. The best interaction from 20 interacting atoms between receptor and ligand of ZINC04923002 was:

Receptor SPT	[3] Strong (primary) hydrogen bond donor H (polar-atom-H)
Ligand SPT	[7] Strong (primary) hydrogen bond acceptor lone pair
Dihedral angle	72.43
Distance	2.6059
Score	-2.4245
Receptor atom	Index:48 Residue: N LYS-101 Type:N
Ligand atom	Index:17 Type:N

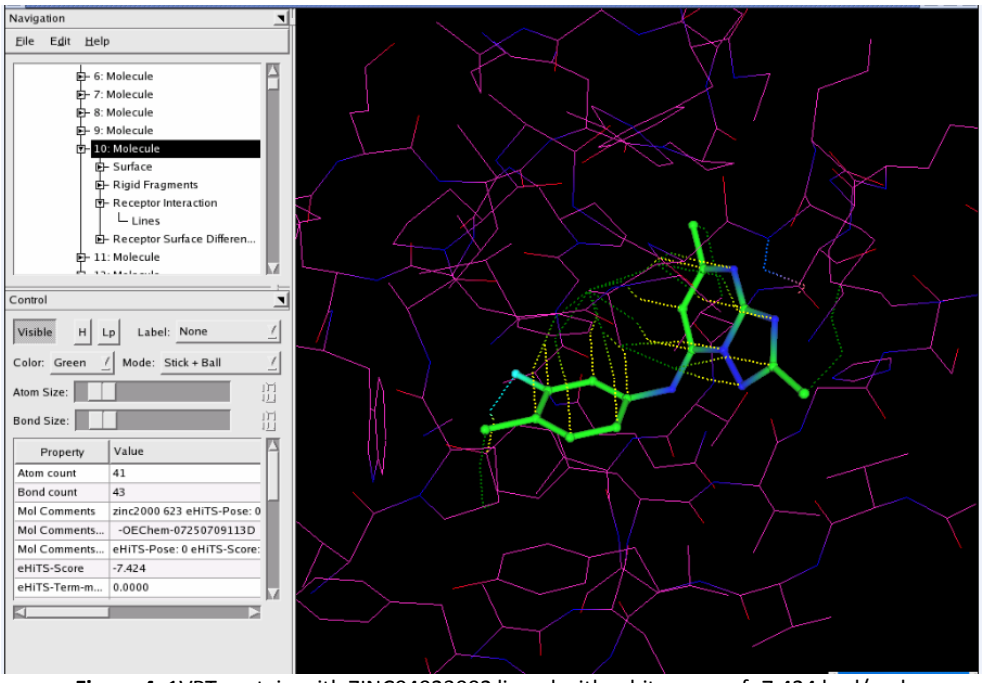

Figure 4. 1VRT protein with ZINC04923002 ligand with e-hits score of -7.424 kcal/mol

In Nevirapine, the major active site residues participated in interactions are: Leu100, Val106, Tyr181, Trp229 and Leu234. Whereas, in ZINC04923148, the majority residue interactions are formed by: Leu100, Lys101, Val179, Tyr181, Tyr188 and Leu234. From the above data, it is evident that the high dock score obtained for ZINC04923148 was due to new residue interactions formed by Lys101 and Tyr188 respectively.

CONCLUSION

Virtual Screening procedure utilized in the study recognized the best molecule than the existing ligand for PDB protein 1VRT resulted in about 59 such molecules from 4.6 million molecule ZINC database. 1VRT bound co-crystallized ligand displayed an e-hits score of -6.5818 kcal/mol. Screening procedures carried out using selected criteria resulted in top three best molecules, represented by ZINC04923148, ZINC05442451 and ZINC04923002 with e-hits scores of -8.179, -7.886 and -7.424 kcal/mol respectively. Therefore, this study states the importance of small molecule libraries and their use to enhance drug discovery process prior synthesis. As exemplified in this case with 1VRT protein of HIV-RT, screening molecules from chemical libraries and the criteria used to screen depends on the number of parameters such as Lipinski's rule of 5, volume and shape of ligand, number of attached groups on ligand, libraries and their search procedures etc.

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