SYNTHESIS OF 1,2,4-TRIAZOLE DERIVATIVES AND ANTI-HIV ACTIVITY BY DOCKING STUDY

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Abstract

Docking was performed using Biopredicta module of V-life MDS demo version. Three molecules showed significant anti-HIV-1 activity were selected for docking with reverse transcriptase enzyme. Docking results indicate that only 1f, molecule have a comparable dock score with reference ligand, because it showed significant H-bonding, hydrophobic, vander waal and additional π-stacking interactions with reverse transcriptase enzyme (2RK-1), Future prospectus of research work. With keeping these points in view, 1f molecule might be considered as a lead molecule on which further substitution might be done to enhance the docking. The result of this study will provide useful information for the design of novel molecules as anti-HIV-1 agents.

Keywords: Docking, anti-HIV- 1 agents, V-life MDS

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I. Introduction

Docking process is started by using demo version of GRIP batch docking in Biopredicta Module of V-life science is used for docking. Docking process is started by using:

(a) 2RK-I: Crystal Structure of HIV-1 Reverse Transcriptase (RT) in Complex with a triazole derived NNRTI

(b) Molecular Design Suite 3.5 – Biopredicta Module

II.Model Development

Step 1. Generation of 2D-Structure of 1f, 3f:

The structures of the said molecules were designed using Chem Draw Ultra 11.0. Saved the same with the extension. *mol.

Step 2. Conversion into 3D- Form of the Biopredicta Module

The molecules were imported in the Molecular design suite and saved as. mol2 file.

Step 3. Labeling of the Molecules:

All the molecules were checked out for their 3D-labelling and shown in Figure 1, 2.

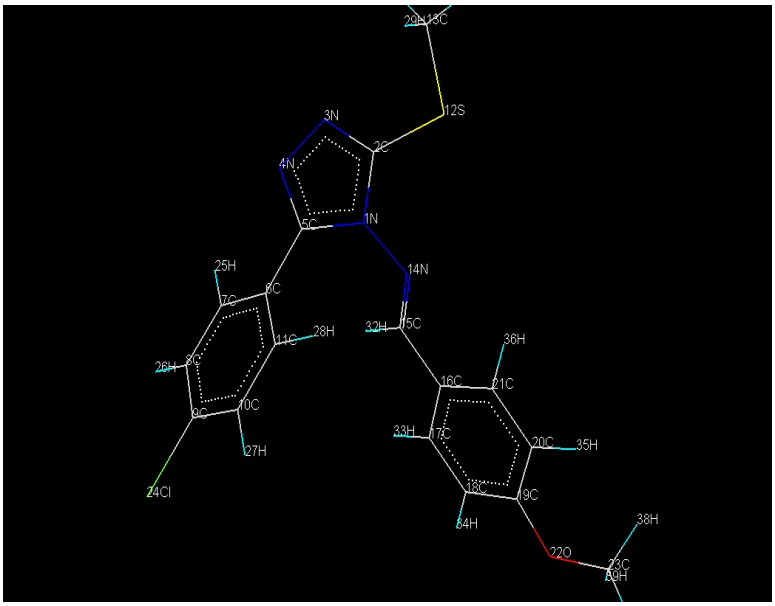

Figure: 1 Labeled Structure of Compound 1f

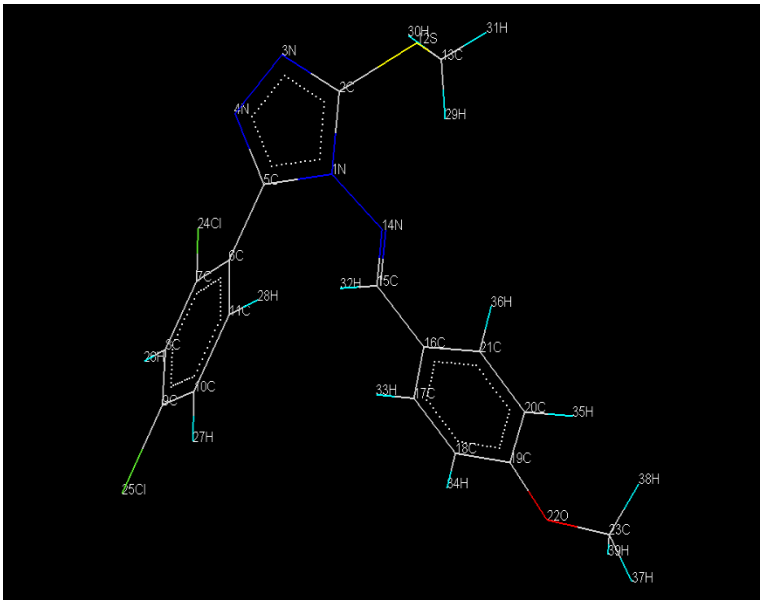

Figure: 2 Labeled Structure of Compound 3f

Step 4: Energy Minimization

The compounds individually subjected to the energy minimization using Merck molecular force field until each compound possesses the minimum energy.

Step 5: Generation of Conformers

Rotatable bonds in any molecule will be responsible for possibilities of various conformers with different energies. Using systemic and monte Carlo method along with the selection of the important rotatable bonds, various conformers were generated. Five conformers from each molecule with minimum energies were selected (Least energy conformers are the stable ones) [Shown in Figure 5,6,7&8].

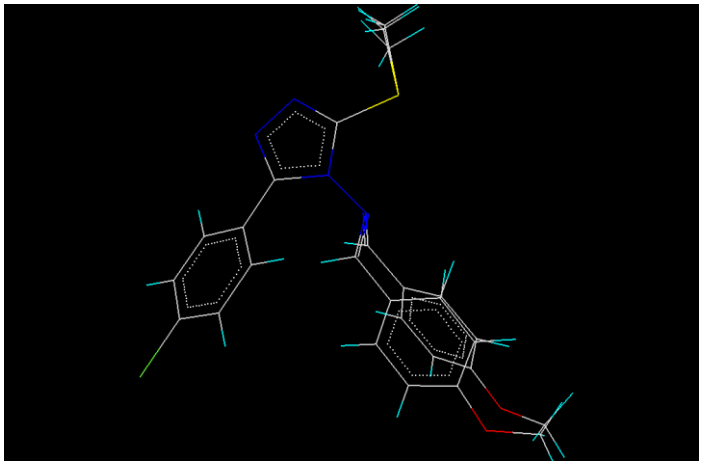

Figure: 5 Alignment of best five conformers of Compound 1f

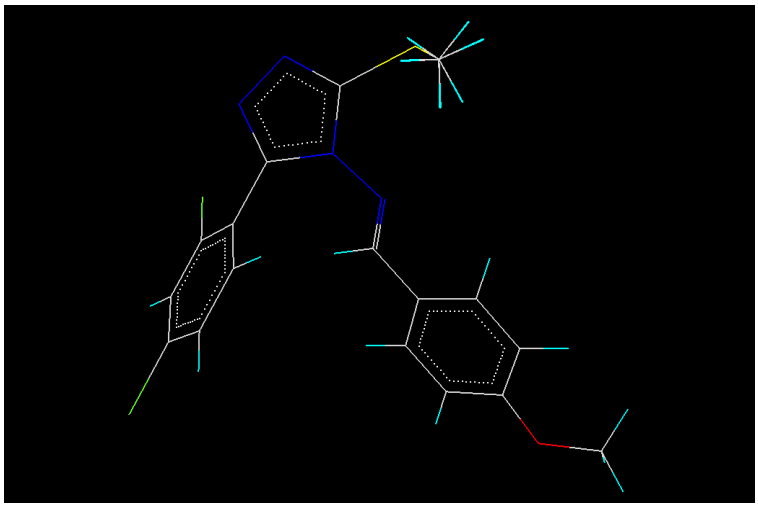

Figure: 6 Alignment of best five conformers of Compound 3f

Step 6: Collecting the 2RK-I

The structure of Human reverse transcriptase enzyme along with co-crystallization of standard 1,2,4-Triazole were taken from the protein data bank with an extension .pdb [Shown in Figure 9 & 10].

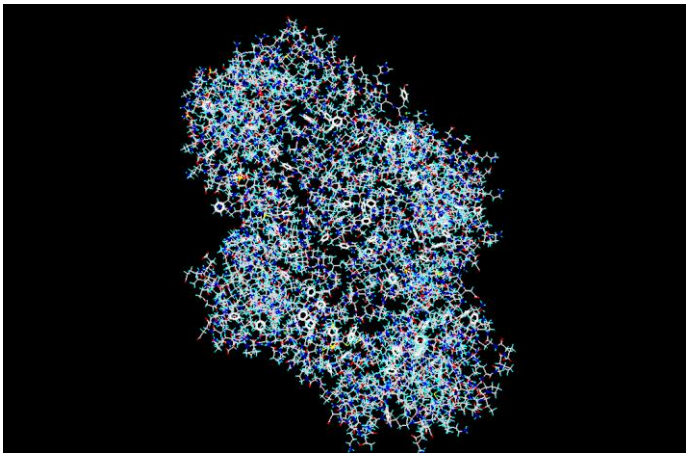

Figure: 9 Crystal Structure of 2RK-I (Co-crystallization of Triazole with Reverse

Transcriptase Enzyme)

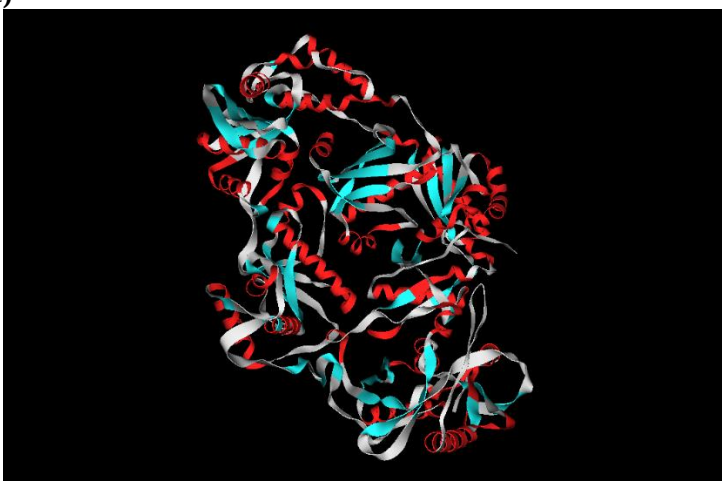

Figure: 10 Tertiary structure of 2RK-I

Step 7: Extraction of Reference Ligand from 2RK-I:
Using the standard procedure, the reference ligand was isolated from the protein and saved as Reference Ligand [Shown in Figure 11]

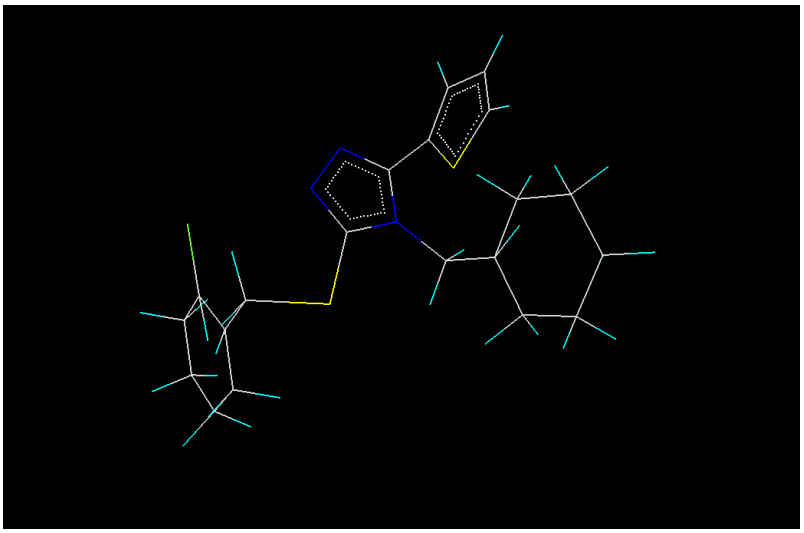

Figure: 11 Standard/Reference Ligand isolated from Co-crystallized Protein 2RK-I

Step 8: Docking Using Robust GRIP Technique
The following steps are required to be done.
a) Selected apo-receptor after extraction of reference ligand from 2RK-I.
b) Selected the Best Conformers.
c) Generated the empty folder with a name output.
d) Selected the reference ligand.
e) Selected parameters as exhaustive, no. of placements as 30 and then started docking.

III. Results & Discussion

After careful observation, it was observed that the reference ligand molecule is having hydrogen bonding, hydrophobic interactions and Vander Waal interactions with the amino acids of the active site present on the 2RK-I.
The H-bonding of reference ligand is with the lysine present at 103 position (Figure 12). Hydrophobic interactions of reference ligand are with proline, tyrosine181A, tyrosine188A, lysine103A, serine105A, valine106A, histidine, leucine, tryptophan (Figure 13). Vanderwaal interactions of reference ligand are with proline, tyrosine, glutamine, valine, Isoleucine, tryptophan, phenylalanine, leucine, serine, glycine (Figure 14).

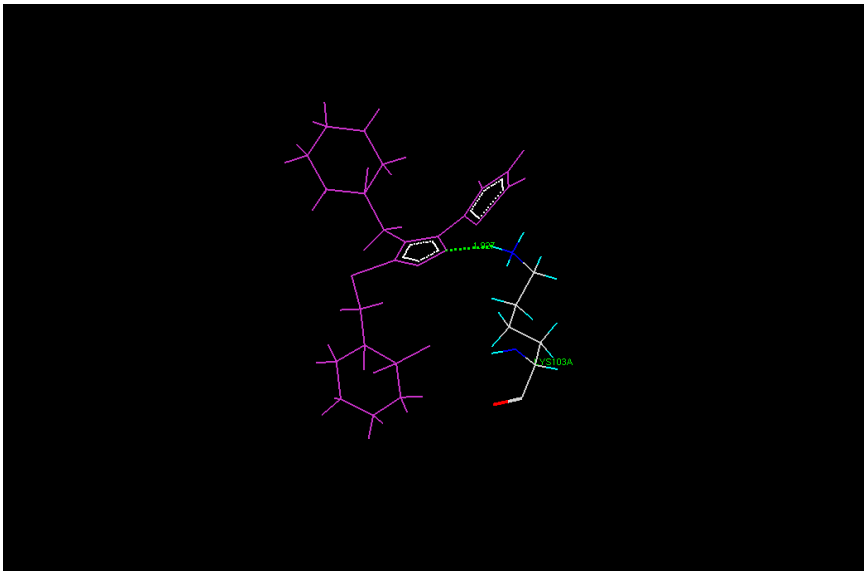

Figure: 12 H Bonding Interaction of Reference Ligand with the amino acid present on the active site of 2RK-I

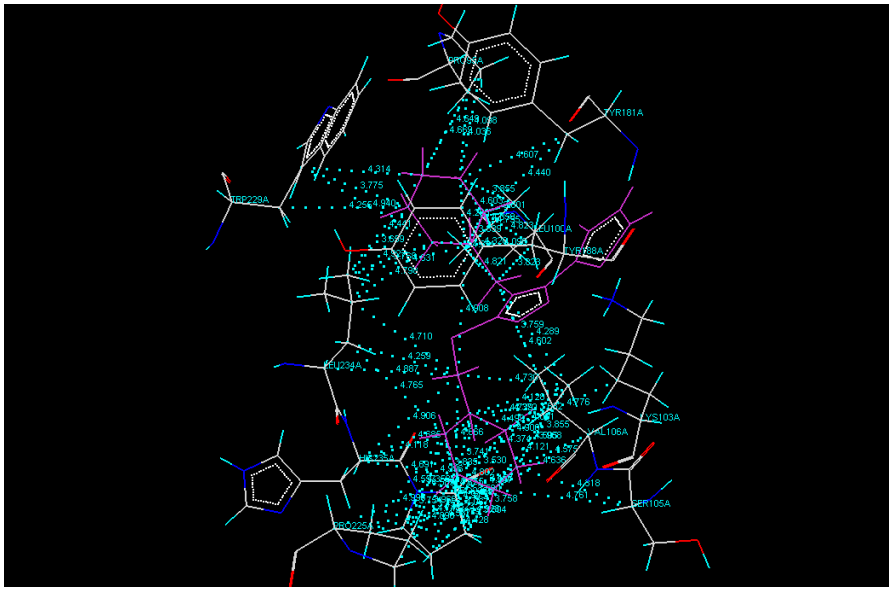

Figure: 13 Hydrophobic interactions of Reference Ligand with the amino acids at the active site of 2RK-I

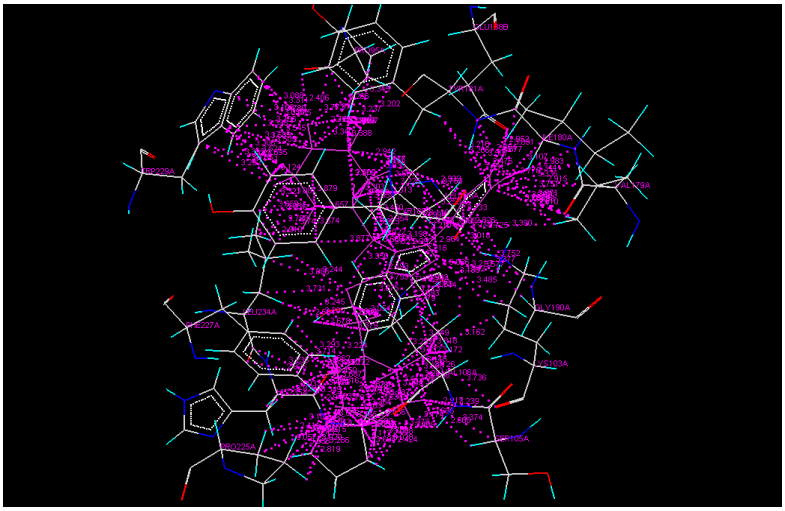

Figure: 14 Vander Waal Interactions of Reference Ligand with the amino acids at the active site of 2RK-I

Compound 1f have hydrophobic, pi-staking and vander waal interactions with the amino acids present on the active site of the reverse transcriptase 2RK-I.

Hydrophobic interactions of 1f molecule are with tryptophan229A, phenylalanine227A, Leucine234A, proline225A, proline236A (Figure 15). 1f molecule is also having a pi-staking interactions with Phenylalanine227 and Tyrosine318 (Figure 16). Vanderwaal interactions of 1f molecule are with tyrosine, Leucine, Phenylalanine, proline, serine, lysine, valine (Figure 17).

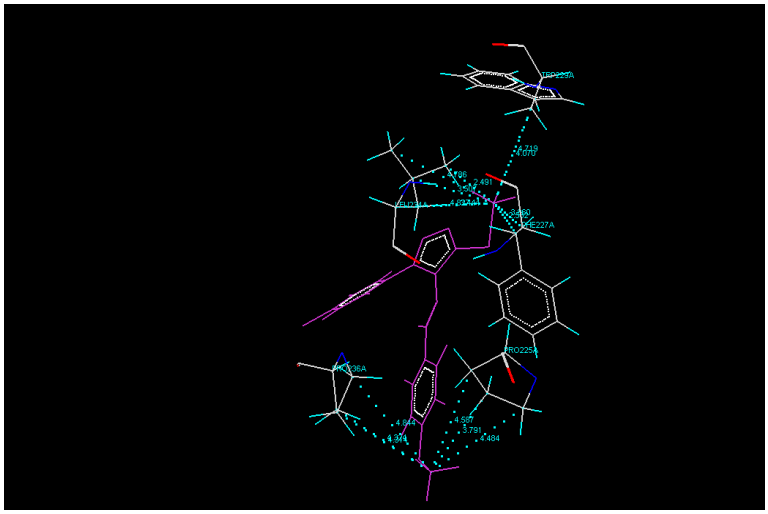

Figure: 15 Hydrophobic Interactions of 1F Molecule with the amino acids at the active site of 2RK-I

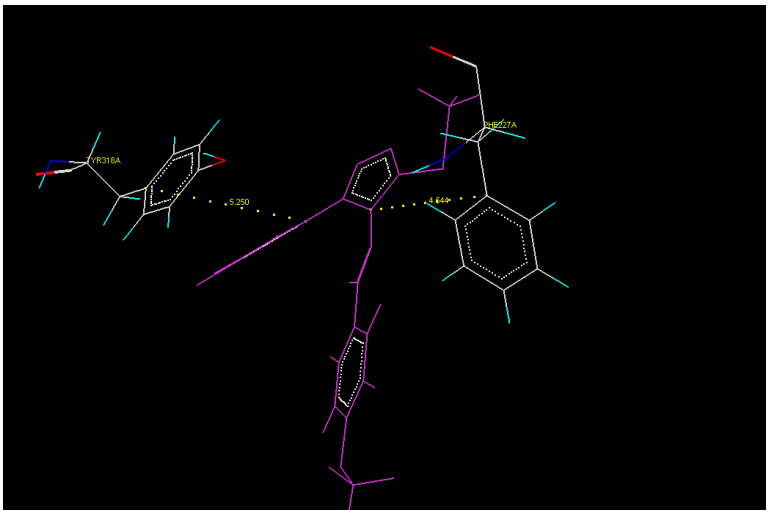

Figure: 16 Pi-Staking interactions of 1F Molecule with the amino acids at the active site of 2RK-I

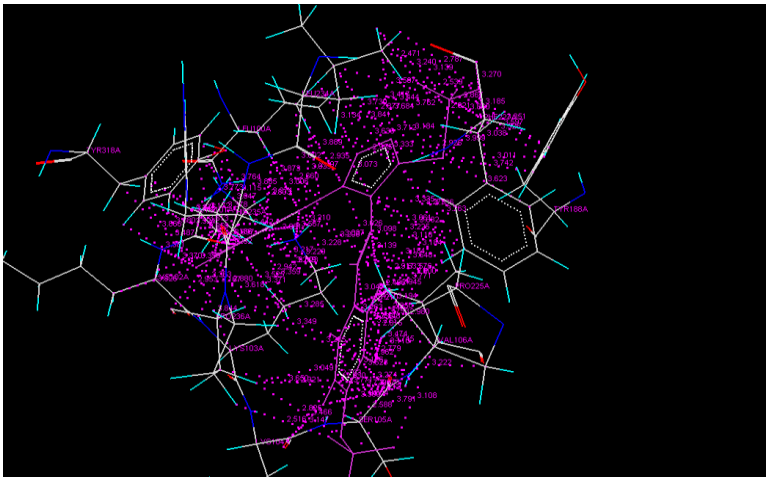

Figure: 17 Vander Waal interactions of 1F Molecule with the amino acids at the active site of 2RK-I

Table: 13 Dock Score of molecules and Reference ligand

S. No	Molecule	Dock Score
1.	min_1f_C949_P30	-46.766997
2.	min_3f_C1021_P22	-15.489900
3.	Reference Ligand	-137.058603

Reference compound is having additional hydrophobic interactions with Lysine and Serine Our reference ligand is having hydrogen bonding with lysine which was present at 103 position, whereas test molecules haven't shown hydrogen bonding with reverse transcriptase enzyme In case of 3f molecules, the interactions are very less and insignificant.

The test molecules have additional pi-staking property except 3f which was not shown by the reference ligand. molecule 1f, have pi-staking property with Phenylalanine and tyrosine residues of the reverse transcriptase. The highest activity of 1f tyrosine residue is of its 318 position and in 3f, it is not present. It also suggests that pi-staking with tyrosine residue of 318 position is not of much significance.

IV. Conclusion

From the above results only 1f, molecule have a comparable dock score with reference ligand with keeping this point in view, 1f molecule can be considered as the parent molecule on which further substitution will be done to enhance the docking. The result of this study will provide useful information for the design of novel molecules as anti-HIV-1 agents.

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