MOLECULAR DOCKING STUDIES OF NOVEL PYRAZOLE ANALOGS AS POSSIBLE HIV-1 RT INHIBITORS

Sony Jacob K[1]* and Swastika Ganguly[2]

[1,2] Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi – 835215, Jharkhand, India.

E.mail. sonyivin@gmail.com (Sony Jacob K); swastikaganguly@bitmesra.ac.in (Swastika Ganguly)

Introduction

➢The human immunodeficiency virus (HIV) is the causative agent of the acquired immunodeficiency syndrome (AIDS)

➢Major reason for the failure of treatment of HIV due to resistance and adverse drug reactions of the current drugs.

➢NNRTIs have the advantage of high potency, low toxicity, high selectivity and specificity.

➢Designing drug- like molecule that can fit to HIV -1 RT will be a promising starting point in developing anti HIV drugs

Objectives

The objective of this study was to elucidate the binding mode analysis of novel pyrazole analogs in the non nucleoside inhibitory binding pocket of reverse transcriptase (PDB ID 1RT2)

Materials and Methods

Docking protocol and their validation

Molecular modeling studies

Molecular modeling studies were performed on workstation running Red Hat enterprise and Linux 4.0 and selection of the compounds depends on the compounds which are obeying Lipinsky rule of five and used an automated docking software Glide 5.0 (Schrodinger-Maestro) that applies a two stage scoring process to sort out the best conformations and orientations of the ligand (defined as pose) based on its interaction pattern with the receptor.

Protein preparation

The starting point of the docking simulation was the X ray structure of the protein, (HIV-1 RT) these are obtained through the protein data bank (PDB) [5]. Chain A was retained, chain B and all the water molecules were removed from the complex. The protein was prepared using the protein preparation wizard. A grid was prepared with the center defined by the co-crystallized ligand TNK 651 for 1RT2 Partial atomic charges are assigned according to the OPLS_AA force field.

Ligand preparation

Three dimensional coordinates of the ligands, their isomeric, ionization and tautomeric states generated using Ligprep. Partial atomic charges were assigned according to the OPLS-2005 force field.

Validation of docking protocol

The most suitable method of evaluating the accuracy of a docking procedure is to determine how closely the lowest energy pose predicted by the scoring function resembles an experimental binding mode as determined by X-ray crystallography. Initially TNK-651 were extracted from the 1RT2 and redocked in to the same. In our previous studies Glide has successfully reproduced the experimental binding conformations of TNK-651 in the NNRTI-binding pocket of HIV -1 RT with an acceptable root-mean-square deviation (RMSD) of 2.4 Å [6]. Glide XP score of TNK651 into active site of NNIBP has been reported as -13.27 [7]. Conformational flexibility of the ligands was handled via an exhaustive conformational search. Initially, Schrodinger Glide scoring function was used in standard precision (SP) mode. Later, top scored compounds were docked again in extra precision (XP) mode to score the optimized poses. The pose were selected based on the hydrophobic, hydrogen bond interactions. Interaction sites of the active ligands with the protein from the docked poses were mapped. The general structure of the designed compounds and reference compound TNK-651 mentioned in **Figure. 1**. The docked complex of **c**ompound 1 in the active site is depicted in **Figure. 2 a** and ligand interaction diagram of compound 1 is depicted in **Figure. 2 b.**

Results and discussion

❖Docking Studies

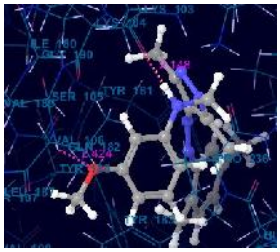

Figure. 2 a. The docked complex of compound 1 in the NNIBP of the 1RT2.Active amino acid residues represented as tubes while the inhibitor represents as ball and stick. Hydrogen bond interaction is represented by pink dotted lines and inter hydrogen atomic distance are also mentioned

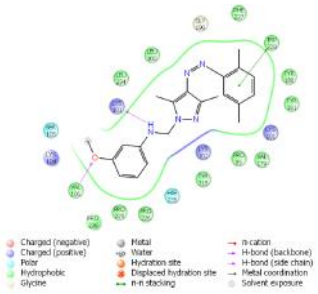

Figure. 2 b. Schematic (2D) representation of interactions of compound **1** in the NNIBP of 1RT2

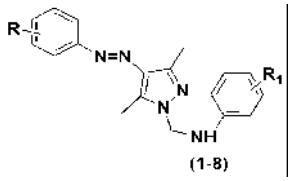

Table 1. Glide XP docking scores of eight pyrazole analogs with highest docking score and that of reference compound TNK-651 in the NNIBP of HIV-1 RT.

Compound code	R	R_1	1RT2
1	2,5-CH_3	m-OCH_3	-13.06
2	H	m-OCH_3	-12.61
3	H	m-CH_3	-12.99
4	o-Cl	m-OCH_3	-12.45
5	o-Cl	p-OCH_3	-12.23
6	m-CH_3	m-CH_3	-12.07
7	m-Cl	m-Cl	-12.06
8	m-Cl	2,4-NO_2	-12.01
TNK-651	-	-	-13.27

Conclusion

Molecular docking studies of 484 pyrazole analogs were performed on NNIBP of HIV-1RT2 by using Glide-5 and eight compounds with substituents like R=2,5-CH_3 &R_1= m-OCH_3, R=H &R_1=m-OCH_3, R=H & R_1=m-CH_3, R=o-Cl &R_1=m-OCH_3, R=o-Cl &R_1=p-OCH_3, R=m-CH_3 &R_1=m-CH_3, R=m-Cl &R_1=m-Cl, R=m-Cl &R_1=2,4-NO_2 exhibited highest docking score in the NNIBP of IRT2.The compounds having highest docking score have been discussed in the present communication. Among theses, visual pose view analysis has been performed for compound 1 which exhibited highest docking score of -13.06 which was comparable to that of reference compound TNK 651. Compound 1 also showed two hydrogen bond interactions in the NNIBP of reverse tanscriptase (PDB ID 1RT2). Thus, from the binding mode analysis as well as docking studies, it is concluded that the newly designed compounds with a pyrazole moiety flanked with phenyl rings which have been substituted with electron donating and electron withdrawing groups showed significant affinity towards the NNIBP of HIV-1 reverse transcriptase compared to the reference drug TNK-651. Thus, this type of scaffold can be exploited for the development of novel HIV-1 RT inhibitors which can facilitate better patient adherence and also inhibit resistant strains of HIV.

Acknowledgements

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