IJPSR (2017), Volume 8, Issue 9 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 28 January, 2017; received in revised form, 12 April, 2017; accepted, 17 April, 2017; published 01 September, 2017

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

Rohit Singh * and Swastika Ganguly

Department of Pharmaceutical Science and Technology, Birla Institute of Technology, Ranchi - 835215, Jharkhand, India.

Keywords:

Imidazole, Non-nucleoside reverse transcriptase inhibitors, Docking, HIV

Correspondence to Author:
Rohit Singh

Research Scholar, Department of Pharmaceutical Science and Technology, Birla Institute of Technology, Ranchi - 835215, Jharkhand, India.

Email: rohitsingh20485bitmesra@gmail.com

ABSTRACT: Molecular docking studies of 102 newly designed N-substituted imidazoles was performed in the non nucleoside inhibitory binding pocket of reverse transcriptase enzyme of wild type as well as resistant strains of HIV-1 virus with PDB ID 1RT2, 1JLB, 3BGR and 1FK9 respectively by using Glide 5.0 to carry out a binding mode analysis of the designed imidazoles. Results generated from this study indicate that most of the compounds dock into the active site of different enzymes such as 1RT2, 1JLB, 3BGR and 1FK9 showing excellent Docking scores comparable to the standard TNK 651. Compounds SRS 21, SRS 34, SRS 45, SRS 46, SRS 73, SRS 76 and SRS 77 exhibited the highest docking scores and were found to be most effective as compared to standard TNK 651.

INTRODUCTION: HIV-1 Reverse Transcriptase: Reverse transcriptase is a key enzyme which plays an important role in the replication of human immunodeficiency virus (HIV-1) and is thus useful in AIDS therapy [1]. Human immunodeficiency virus, also called retrovirus, has two subtypes *i.e.* HIV-1 (occurs worldwide) and HIV-2 (found mainly in Africa), consist of a single stranded RNA genome which is converted into double stranded DNA. This conversion occurs in the cytoplasm of newly HIV infected cell in the presence of a viral enzyme named as reverse transcriptase [2]. The currently available drugs for AIDS therapy are protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [3, 4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(9).3751-57

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (9).3751-57

The currently available drugs for AIDS therapy are protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [3, 4]. Unlike nucleoside analogs, non nucleoside reverse trancriptase inhibitors (NNRTI's) bind in a non-competitive manner to a specific pocket of HIV-1 RT and alters the viral replication mechanism by acting as a chain terminator [5, 6]. From the literature survey, it was observed that the butterfly like shape is important factor in the binding of the first generation NNRTIs.

Despite their chemical diversity, they assume very similar butterfly-like shape. The butterfly structure has a hydrophilic centre as a 'body' and two hydrophobic moieties representing the 'wings' [7]. X-ray crystallographic studies reveals that NNRTI's posses's butterfly like' conformation and appear to function as pi electron donors surrounding binding pocket. Presently three NNRTI's namely nevirapine, delavirdine, and efavirenz are commercially available in clinical

practice. Combination of these NNRTI's with NRTI's and protease inhibitors (PI's) are used in the treatment of most cases of HIV infected patients. Three NNRTIs, nevirapine (Viramune1), delavirdine (Rescriptor1) and efavirenz (Sustiva1, Stocrin1) were approved for the treatment of HIV infection in 1996, 1997 and 1998, respectively. They became cornerstones of HIV therapy because of their full potential as a component of HAART [8]. Nevirapine is also one of the few agents that are used to prevent mother-to-child transmission of HIV. In contrast to NtRTIs, they display a unique anti-retroviral activity spectrum that is limited to HIV-1 only.

The NNRTIs are non-competitive inhibitors that bind allosterically to an asymmetric and hydrophobic cavity, about 10 A° away from the catalytic site of the HIV-1 RT [9]. As a result of NNRTI binding, certain RT domains that actively participate in DNA synthesis are restricted in flexibility and mobility which, in turn, leads to a dramatic reduction in catalytic enzyme efficiency [10]. Recent studies also point to the interplay between the NRTI and NNRTI binding sites, possibly explaining the synergies between the two classes of RT inhibitors. Nevirapine (NNRTI) was one of the first medicaments with anti-retroviral activity to be treated against humans but that led to a rapid development of resistance associated with loss in clinical efficacy. The main side effect of nevirapine is the appearance of rashes, which are toxic in nature and in few cases Steven Johnson have been reported. While delavirdine and efavirenz generally used in combination and the main side effects are rashes, nausea, and loss of apetite, insomnia and strange dreams.

The NNRTIs nevirapine, delavirdine, and efavirenz (**Scheme 1**) have been approved for treatment of HIV-1 infection in combinations with other RT and non-RT drugs. As with all classes of anti-HIV-1 drugs, resistant viral strains evolve which severely impair the long-term efficacy of the NNRTIs. This limits the usefulness of NNRTI's [11]. Current anti-AIDS therapy is based on drugs that belong either to the class of nucleoside/nucleotide (NRTIs / NtRTIs) and non-nucleoside reverse transcriptase inhibitors. The nucleoside (seven drugs) and nucleotide (one drug) analogues (collectively known as nucleoside reverse transcriptase inhibitors [NRTIs] and nucleotide reverse transcriptase inhibitors [NtRTIs], respectively) are activated by host enzymes to their triphosphate forms, which bind to the active site of RT, where, acting as substrate decoys, they pre-terminate DNA chain elongation during viral DNA synthesis (**Fig. 1**). (NNRTIs), protease, or entry inhibitors. NNRTIs area structurally diverse group of compounds which interact with a specific allosteric non-substrate binding pocket site of HIV-1 RT (non-nucleoside inhibitor binding pocket), leading to a non-competitive inhibition of the enzyme [12].

Docking Strategies: Knowledge of the three-dimensional (3D) structure of ligand + protein complexes provides a valuable understanding of the function of molecular systems. The rate of protein structure determination is increasing rapidly. Today there are some 5,000 entries in the Brookhaven Protein Data Bank [13]. The number of ligands available to assess and rationalize ligand protein interactions is large. Assuming the receptor structure is available, a primary challenge in lead discovery and optimisation is to predict both ligand orientation and binding affinity; the former is often referred to as 'molecular docking'. Docking methodologies with novel extensions, and the diversity in both their complexity and computational speed provides a plethora of techniques to tackle modern structure based drug design problems [14, 15]. The importance of docking in the field of drug design is that it increases computer power and docking performance, it is now possible to dock thousands of ligands in a timeline which is useful to the pharmaceutical industry [16].

The non-nucleoside inhibitory binding pocket (NNIBP) is mainly a hydrophobic pocket that contains side chains of aromatic amino acid residues Y181, Y188, F227, W229 and Y318 and of hydrophobic amino acid residues P95, L100, V106, V108, V179, L234 and P236 from the p66 subunit [17].

MATERIAL AND METHOD:

Computational Docking Study by Glide 5.0 (Schrodinger lnc; USA): Docking study was performed for all designed compounds (1-102) by glide 5.0 version (ref. schrodinger lnc USA schrodinger LLC Newyork 2008) installed in a single machine running on a 3.4 GHZ Pentium 4 processor with 1 GB RAM and 160 GB hard disk

with red hat linux enterprise version 8.5 as operating system.

Protein Structure Preparation: The X-ray crystallographic structure of HIV-1 RT complexed with TNK-651(PDB entry code 1RT2), Y181C mutant HIV-1 reverse transcriptase complexed with Nevirapine (PDB entry code 1JLB), Bis heteroaryl piperazine U-90152 (BHAP-U) resistant mutation for HIV-1 RT (PDB entry code 1KLM), K103N/Y181C mutant HIV-1 RT complex with TMC 278 (Rilvirapine) etc were obtained from brookhaven protein data bank (RCSB) [8]. (ref. http:// www.rcsb.org/pdb) for glide docking studies, chain A was retained and all water molecules as well as chain B were removed and missing hydrogen atom were added and structure was optimized since tnk crystallized ligand in the enzyme HIV-1 RT complexed with Tnk-651. 3BGR crystal structures of k103N/Y181C mutant HIV-1 RT in complex with TMC 278 (rilpivirine) which is a nucleoside reverse transcriptase inhibitor.

TMC 278 is a diaryl pyrimidine (DAPY) non nucleoside reverse transcriptase in complex with Nevirapine (PDB entry code 1JLB) and HIV-1 reverse transcriptase complexed with BHAPU-90152 (bis heteroaryl piperazine) (PDB entry code 1KLM).

Ligand Structure Preparation: All the designed substituted imidazole compound used in docking study were prepared with glide in maestro 8.5 version of schrodinger Inc. these structures were geometrically optimized potentials for liquid simulations_2005 (OPLS_2005) force field. Partial atomic charges were computed using the OPLS_2005 force field.

Receptor Grid Generation: Shape and properties of receptor were represented on a grid by different set of fields that provide progressively more accurate scoring of ligand poses. Pick the ligand molecule and that was excluded from receptor grid generation. After that scaling of vanderwaals radii of non polar atoms which gave better interaction between receptor and ligand. Scaling of other interaction can also help to model flexibility of parts of the receptor. Appropriate method to determine how closely ligand bound with the receptor during docking procedure.

Docking Study: In this study, docking of TNK 651, Nevirapine, BHAP and Rilpivirine were extracted from protein 1RT2, 1JLB, 1KLM and 3BGR performed to dock with prepared respective proteins in order to dock with prepared respective proteins in order to check reliability and reproducibility of docking protocol for our study. A very good interaction were found between ligand their particular receptor.SH imidazole ring with carbonyl group of lysine and 'N' heteroatom of imidazole with hydrogen bond that was 1.909 A° and 2.262 A° respectively which were shown in **Fig. 1A** and **1B**.

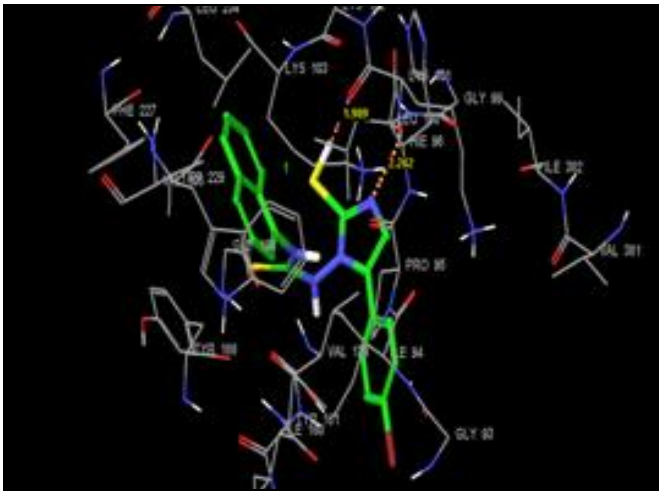

FIG. 1A: MOLECULAR MODEL OF IMIDAZOLE A SERIES (73) IN THE NNRTI OF HIV-1 RT (PDB CODE 1RT2)

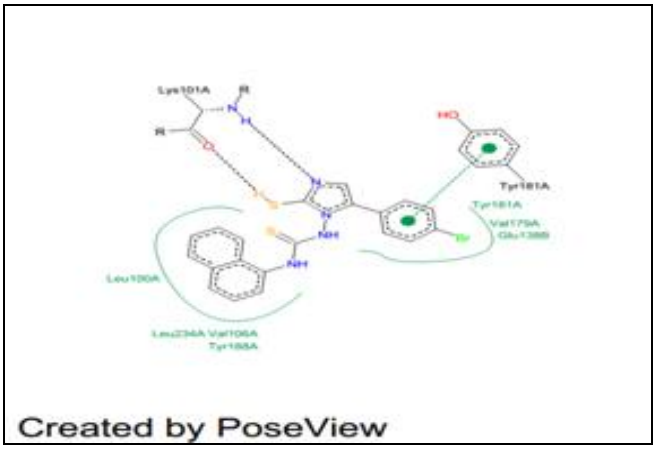

FIG. 1B: SCHEMATIC (2D) REPRESENTATION OF INTERACTIONS OF COMPOUND 73 IN THE BINDING POCKET OF THE PROTEIN

Active site amino acid residues are represented as lines while the inhibitor is shown as ball and stick model with the atoms colored as carbon: green, hydrogen: cyan, nitrogen: blue, and oxygen: red. Hydrogen bond interactions are represented by pink dotted lines. ($SH_{IMIDAZOLE\ RING}$ ___CO_{LYS101} =

1.909 A° and N of imidazole ring_NH_{LYS101} = 2.262 A°). Put the distance of H bond interactions as shown in sample here (Glide XP Score - 12.47).

The root mean square deviation (RMSD) between extracted ligand and crystallized receptor was carried out by redocking extracted ligand Nevirapine, BHAP, and Relpivirine into the active site of 1JLB, 1KLM and 3BGR. The RMSD found for 1JLB, 1KLM and 3BGR were a series of designed imidazole derivative analogs (1-102) were used for molecular docking studies on active site of different proteins *viz* 1RT2, 1JLB, 1KLM and 3BGR by using glide 5.0.

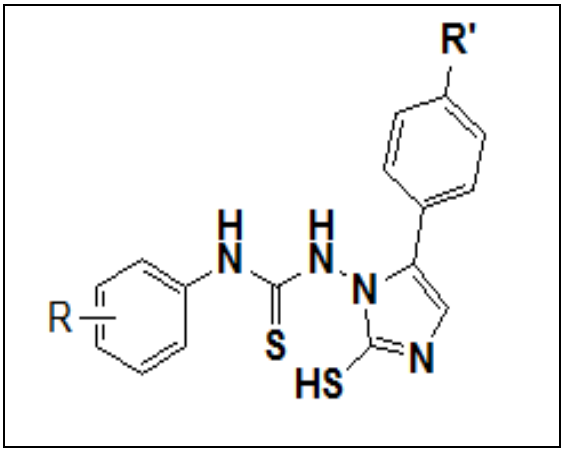

FIG. 2: ??

TABLE 1: THE DOCKING SCORES

Compound no.	R	R'	Dock score on 1RT2	1JLB	1KLM	3BGR
SRS 1	H	Br	-9.27	-6.83	-8.69	-5.89
SRS 2	H	Cl	-9.81	-8.31	-9.11	-11.59
SRS 3	H	CH_3O	-10.55	-6.92	-8.69	-6.66
SRS 4	H	CH_3	-8.76	-7.37	-11.74	-11.58
SRS 5	H	NO_2	-8.92	-6.60	-9.97	-7.19
SRS 6	H	C_6H_5	-11.11	-7.36	-7.33	-7.66
SRS 7	3-Cl	Br	-8.54	-5.88	-9.94	-11.29
SRS 8	3-Cl	Cl	-8.69	-5.08	-12.02	-12.00
SRS 9	3-Cl	CH_3O	-9.06	-6.60	-10.05	-9.18
SRS 10	3-Cl	CH_3	-10.34	-5.35	-11.78	-9.52
SRS 11	3-Cl	NO_2	-8.99	-5.52	-9.58	-8.66
SRS 12	3-Cl	C_6H_5	-9.90	-5.34	-9.17	-7.77
SRS 13	4-Cl	Br	-8.78	-5.48	-9.89	-7.87
SRS 14	4-Cl	Cl	-9.85	-6.42	-10.85	-10.91
SRS 15	4-Cl	CH_3O	-9.68	-6.04	-9.76	-10.11
SRS 16	4-Cl	CH_3	-9.80	-4.85	-9.58	-11.88
SRS 17	4-Cl	NO_2	-10.01	-7.27	-10.06	-8.19
SRS 18	4-Cl	C_6H_5	-10.77	-6.43	-9.52	-7.61
SRS 19	2-CH_3	Br	-8.66	-7.78	-8.56	-8.78
SRS 20	2-CH_3	Cl	-9.14	-6.54	-11.71	-6.47
SRS 21	2-CH_3	CH_3O	-12.02	-7.15	-9.07	-6.64
SRS 22	2-CH_3	CH_3	-11.25	-5.88	-9.17	-11.22
SRS 23	2-CH_3	NO_2	-9.47	-6.61	-9.43	-11.93
SRS 24	2-CH_3	C_6H_5	-9.22	-5.66	-8.59	-6.64
SRS 25	4-CH_3	Br	-10.04	-3.85	-10.23	-11.22
SRS 26	4-CH_3	Cl	-10.02	-6.54	-10.82	-11.93
SRS 27	4-CH_3	CH_3O	-9.95	-6.03	-10.17	-9.99
SRS 28	4-CH_3	CH_3	-9.77	-6.49	-10.61	-8.40
SRS 29	4-CH_3	NO_2	-9.80	-5.63	-10.23	-6.92
SRS 30	4-CH_3	C_6H_5	-8.50	-6.49	-7.36	-7.64
SRS 31	2-NO_2	Br	-8.29	-5.75	-8.87	-8.25
SRS 32	2-NO_2	Cl	-8.54	-5.67	-8.40	-8.39
SRS 33	2-NO_2	CH_3O	-8.94	-5.61	-8.46	-8.03
SRS 34	2-NO_2	CH_3	-12.11	-5.51	-8.16	-8.42
SRS 35	2-NO_2	NO_2	-8.63	-5.64	-8.62	-6.03
SRS 36	2-NO_2	C_6H_5	-6.82	-7.29	-7.23	-8.02
SRS 37	4-NO_2	Br	-8.58	-3.17	-11.64	-10.93
SRS 38	4-NO_2	Cl	-8.45	-7.11	-12.15	-11.27
SRS 39	4-NO_2	CH_3O	-8.09	-7.32	-11.64	-8.21
SRS 40	4-NO_2	CH_3	-8.62	-4.45	-12.30	-11.03
SRS 41	4-NO_2	NO_2	-8.68	-5.81	-10.94	-4.09
SRS 42	4-NO_2	C_6H_5	-7.12	-2.73	-7.35	-7.52

SRS 43	3-Cl,2-CH_3	Br	-10.03	-6.74	-10.28	-9.24
SRS 44	3-Cl,2-CH_3	Cl	-11.15	-6.83	-9.79	-9.43
SRS 45	3-Cl,2-CH_3	CH_3O	-12.14	-4.86	-9.71	-7.35
SRS 46	3-Cl,2-CH_3	CH_3	-12.07	-4.08	-9.54	-8.36
SRS 47	3-Cl,2-CH_3	NO_2	-10.79	-7.06	-10.50	-8.08
SRS 48	3-Cl,2-CH_3	C_6H_5	-7.39	-6.62	-9.03	-7.84
SRS 49	2-Cl-6-CH_3	Br	-9.82	-5.94	-9.04	-8.50
SRS 50	2-Cl-6-CH_3	Cl	-6.49	-8.40	-9.61	-8.85
SRS 51	2-Cl-6-CH_3	CH_3O	-5.98	-6.28	-9.08	-8.36
SRS 52	2-Cl-6-CH_3	CH_3	-6.88	-8.05	-9.38	-9.07
SRS 53	2-Cl-6-CH_3	NO_2	-9.74	-5.57	-9.35	-7.81
SRS 54	2-Cl-6-CH_3	C_6H_5	-6.41	-5.13	-7.80	-7.76
SRS 55	3,4-di-Cl	Br	-11.00	-7.85	-9.54	-7.38
SRS 56	3,4-di-Cl	Cl	-11.00	-6.33	-10.94	-6.46
SRS 57	3,4-di-Cl	CH_3O	-11.36	-7.91	-11.52	-7.91
SRS 58	3,4-di-Cl	CH_3	-5.67	-8.23	-10.54	-8.16
SRS 59	3,4-di-Cl	NO_2	-9.84	-6.28	-9.79	-7.11
SRS 60	3,4-di-Cl	C_6H_5	-8.60	-6.44	-9.66	-7.95
SRS 61	4-Br	Br	-10.23	-3.50	-11.76	-10.89
SRS 62	4-Br	Cl	-8.33	-4.83	-12.12	-10.42
SRS 63	4-Br	CH_3O	-9.20	-6.16	-9.20	-9.47
SRS 64	4-Br	CH_3	-6.23	-6.05	-11.61	-11.82
SRS 65	4-Br	NO_2	-9.10	-5.79	-10.38	-7.09
SRS 66	4-Br	C_6H_5	-7.84	-6.50	-9.05	-8.00
SRS 67	2,5-di-CH_3	Br	-10.04	-6.99	-9.64	-7.61
SRS 68	2,5-di-CH_3	Cl	-10.38	-4.38	-9.60	-8.46
SRS 69	2,5-di-CH_3	CH_3O	-10.55	-5.02	-10.59	-8.02
SRS 70	2,5-di-CH_3	CH_3	-7.71	-7.09	-9.61	-8.32
SRS 71	2,5-di-CH_3	NO_2	-10.18	--6.91	-9.94	-7.57
SRS 72	2,5-di-CH_3	C_6H_5	-7.00	-5.94	-8.99	-6.54
SRS 73	α- napthyl	Br	-12.47	-9.94	-8.73	-10.26
SRS 74	α- napthyl	Cl	-9.73	-9.74	-11.81	-10.32
SRS 75	α- napthyl	CH_3O	-8.69	-9.59	-8.47	-9.54
SRS 76	α- napthyl	CH_3	-12.21	-8.57	-8.67	-9.59
SRS 77	α- napthyl	NO_2	-12.04	-8.94	-8.88	-9.54
SRS 78	α- napthyl	C_6H_5	-9.23	-3.25	-10.91	-10.27
SRS 79	4-O CH_3	Br	-6.83	-6.30	-8.88	-11.16
SRS 80	4-O CH_3	Cl	-8.65	-6.57	-8.47	-7.94
SRS 81	4-O CH_3	CH_3O	-8.14	-3.90	-8.67	-7.94
SRS 82	4-O CH_3	CH_3	-5.76	-7.01	-7.87	-11.74
SRS 83	4-O CH_3	NO_2	-8.07	-5.32	-10.43	-7.44
SRS 84	4-O CH_3	C_6H_5	-0.58	-4.79	-7.65	-8.15
SRS 85	3,4-di-CH_3	Br	-10.12	-6.28	-10.52	-11.80
SRS 86	3,4-di-CH_3	Cl	-7.26	-7.81	-10.96	-12.02
SRS 87	3,4-di-CH_3	CH_3O	-10.32	-7.08	-10.86	-10.17
SRS 88	3,4-di-CH_3	CH_3	-9.20	-5.52	-11.44	-12.02
SRS 89	3,4-di-CH_3	NO_2	-7.96	-5.70	-10.99	-7.14
SRS 90	3,4-di-CH_3	C_6H_5	-11.00	-4.62	-9.55	-7.99
SRS 91	2,4,5-tri-Cl	Br	10.56	-7.53	-10.03	-9.23
SRS 92	2,4,5-tri-Cl	Cl	-10.34	-6.12	-10.74	-9.13
SRS 93	2,4,5-tri-Cl	CH_3O	-11.62	-7.82	-10.36	-8.36
SRS 94	2,4,5-tri-Cl	CH_3	-8.48	-6.69	-9.48	-8.40
SRS 95	2,4,5-tri-Cl	NO_2	-10.64	-4.68	-9.90	-7.05
SRS 96	2,4,5-tri-Cl	C_6H_5	-7.83	-4.86	-9.21	-8.60
SRS 97	2,4-di-CH_3	Br	-7.52	-6.34	-9.84	-7.98
SRS 98	2,4-di-CH_3	Cl	-10.09	-5.96	-10.06	-8.44
SRS 99	2,4-di-CH_3	CH_3O	-10.25	-5.92	-9.60	-6.51
SRS 100	2,4-di-CH_3	CH_3	-9.97	-6.14	-9.84	-8.60
SRS 101	2,4-di-CH_3	NO_2	-8.11	-6.49	-9.62	-7.38
SRS 102	2,4-di-CH_3	C_6H_5	-7.26	-6.22	-7.53	-6.12

RESULTS AND DISCUSSION:

Docking studies: A large number of HIV protein crystal structures have been reported in the literature which has different conformations. In this work we have considered four crystal structures (PDB ID: 1RT2, 1JLB, 3BGR and 1FK9) that are co-crystallized with inhibitors TNK 651, Nevirapine, BHAP and Rilpivirine respectively. Docking studies were performed using Glide v5.0 on four high resolution crystal structures of HIV protein with their binding modes of quality and molecular interactions between differently substituted imidazole analogs and results of which are depicted in **Table 1**.

The reliability of the docking results was first checked by comparing the best docking poses obtained for the co-crystallized inhibitor with its bound conformation. This was done by removing each ligand from their active site and subjecting again to redocking into the binding pocket in the conformation found in the crystal structure. As a result, a root mean square deviation (RMSD) of 1.728 A°, 1.142 A°, 1.248 A° and 2.001 A° for HIV proteins PDB ID: 1RT2, 1JLB, 3BGR and 1FK9 co-crystalized TNK 651, Nevirapine, BHAP and Rilpivirine respectively were found suggesting that the docking procedure could be relied onto predict the binding mode of our compounds.

The X-ray structure of the HIV-protein cocrystallized with TNK-651 was taken from the protein data bank; PDB ID 1RT2. The HIV protein binding site contains the important residues Lys 101A, Tyr 101A, Leu 100A, Val 106A, Tyr 188A, Tyr 181A Val 179A and Glu 138 B. The imidazole scaffold is favourably embedded in the hydrophobic pocket surrounded by the side chains of Leu 101 A, Tyr 101 A and Val 106 A. The compound also shows one H-bond interaction between the hydrophilic spacer group $SH_{IMIDAZOLE\ RING}$ ___CO_{LYS101} = 1.909 A° and N of imidazole ring_NH_{LYS101} = 2.262 A°.

These interactions may be responsible for the binding affinity of the molecule as indicated by the docking scores - 12.47 comparable and more than the docking score - 12.04 of the reference ligand Tnk 651.

CONCLUSION: A number of newly designed imidazole analogs 1 - 102 were docked into the active sites of four crystal structures of HIV protein (PDB ID 1RT2, 1JLB, 3BGR and 1FK9) in order to investigate the possible interactions between the designed imidazole analogs and the active site of the non nucleoside reverse transcriptase protein HIV inhibitor protein. The binding mode analysis of the compounds with the highest docking scores was carried out and was compared with that of the co-crystallized ligands and co-crystalized TNK 651, Nevirapine, BHAP and Rilpivirine respectively.

It was found that compound 73 showed the highest docking score - 12.47 in the active site of the HIV protein of 1RT2. Compound 73 exhibited one hydrogen bond interaction and the dock score (- 12.47) was also higher than that of the reference standard TNK 651 (- 12.04) while compound 76, compound 77, compound 34, compound 45 and compound 90 showed highest docking score of - 12.21, - 12.07, - 12.14, - 12.11 and - 11.90 respectively in the active sites of various HIV proteins.

ACKNOWLEDGMENT: The authors acknowledge University Grants Commission for providing financial support in the form of a Major Research Project. One of the authors (RS) thankfully acknowledges the University Grants Commission - Major Research Project (UGC-MRP) for the award of fellowship during the work.

CONFLICT OF INTEREST: Authors declare no conflict of interest.

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How to cite this article:
Singh R and Ganguly S: Molecular docking studies of novel imidazole analogs as HIV-1-RT inhibitors. Int J Pharm Sci Res 2017; 8(9): 3751-57.doi: 10.13040/IJPSR.0975-8232.8(9).3751-57.