www.sphinxsai.com

International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 974-984, Oct-Dec 2009

DOCKING STUDIES OF SOME NOVEL 1-{2-(DIARYLMETHOXY) ETHYL]-2-METHYL-5-NITROIMIDAZOLE (DAMNI) ANALOGS

Swastika Ganguly* and Naresh Panigrahi†
Dept. of Pharmaceutical Sciences, Birla Institute of Technology, Mesra,Ranchi -835215, Jharkhand, INDIA.
Corres.author: swastikaganguly@bitmesra.ac.in

ABSTRACT. Protein-Ligand docking has been used as an important tool in computer aided drug design and inhibitor design. In the present study, 68 novel 1-{2-(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazole (DAMNI) analogs were docked into the Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) binding pockets of HIV-1 reverse transcriptase (RT) structure with PDB ID 1rt2 by using Glide v 5.0 and Scigress Explorer Ultra 7.7 software. The docking scores were correlated with the actual pEC_{50} for each software. Among these, compounds 23 and 9 showed the maximum free binding energy of -13.44 and -116.21 kcal/mol according to prediction by Glide and Scigress Explorer respectively. The docking results indicate that the novel 1-{2-(diarylmethoxy) ethyl]-2-methyl-5-nitroimidazole (DAMNI) analogs adopt a butterfly like conformation in the NNIBP with the imidazolyl group with the CH_2CH_2O side chain as the hydrophilic group surrounded by two aryl hydrophobic moieties, one of which is substituted with smaller hydrophobic groups while the methyl and the nitro group at the 2nd and 5th position of the imidazole nucleus are crucial for activity of the DAMNI analogs. A correlation coefficient of 0.8761 r and 0.7675 r^2 between experimental pEC_{50} and docking scores was obtained with Scigress Explorer while a correlation coefficient 0.24718 r and 0.061 r^2 between experimental pEC_{50} and XP docking scores was obtained using Glide, thus suggesting the effectiveness of Scigress Explorer as an effective desktop molecular modelling tool.

KEY WORDS. HIV-1 reverse transcriptase (HIV-1 RT); Non-nucleoside reverse transcriptase inhibitor (NNRTI); Docking; 1-{2-(diarylmethoxy) ethyl]-2-methyl-5-nitroimidazole (DAMNI).

INTRODUCTION

Human Immuno deficiency Virus (HIV) has been identified as the probable causative agent for Acquired Immuno deficiency Syndrome (AIDS). HIV-1 is a retrovirus, i.e., single stranded RNA virus that utilizes an enzyme known as DNA polymerase or reverse transcriptase (RT) to produce a double stranded DNA provirus that is able to insert itself into the host DNA[1]. Because of the crucial role of RT to HIV replication, inhibition of this enzyme is one of the major potential attractive targets in the treatment of AIDS. In general, the inhibitors of HIV-1 RT are classified into two main categories: nucleoside/nucleotide inhibitors (NRTIs) and non-nucleoside inhibitors (NNRTIs), depending upon their mechanism of action. NRTIs are substrate analogs of normal nucleotides that act competitively at the catalytic site of HIV-1 RT and there by terminating DNA synthesis, whereas NNRTIs are a chemically diverse group of compounds that noncompetitively bind to the unique allosteric hydrophobic binding pocket located about 10 Å away from the RT DNA polymerase active catalytic site and 60 Å from the RT RNase H active site and thereby force the RT subunits into an inactive conformation[2].

When compared to NRTIs, NNRTIs have the advantage of high potency, low toxicity, high selectivity and specificity[3]. Nevertheless this real advantage is vanished due to cross resistance displayed by all approved NNRTIs. To overcome these difficulties novel NNRTIs are searched by modifying the existing drug classes with appropriate pharmacophoric requirements. Earlier studies reveals that, most of the NNRTIs have some features in common, that is, the overall structure may be considered reminiscent of a butterfly with hydrophilic centre ('body') and two hydrophobic outskirts ('wings')[4].

Computational methods have developed into useful tools in the area of new drug discovery. These methods are simple and non-expensive and speed up the process of designing novel and potent molecules with desired biological activity. Docking is one of the commonly used computational method in structure based drug design [5,6]. Docking is the process of fitting of the ligand into the

receptor. It not only give an idea about how the ligand is going to bind with the receptors but also about up to what extent conformational changes can be brought in the receptor structure . Docking comprises two distinct tasks, the first being the prediction of favorable binding geometries for a small molecule in the binding site of a target protein and secondly, the estimation of the binding free energy of the complex so formed, also referred to as scoring.

Docking accuracy reflects an algorithm's ability to discover a conformation (pose) and alignment of a ligand relative to a cognate protein that is close to that experimentally observed and to recognize the pose as correct. Scoring accuracy is the ability to correctly predict the rank order of binding affinities of ligands to a particular protein[7].

Compounds having Nitroimidazole moiety exhibit potent antiprotozoal [8-11] and antibacterial[12-17], activities and many of them are well established in clinical practice. Recently a novel series of 1-{2-(diarylmethoxy) ethyl]-2-methyl-5-nitroimidazole DAMNI analogs have been found to exhibit antiHIV activities [18-20]. In view of these facts and in our continued interest in nitroimidazoles, we wish to report the docking studies of novel 1-{2-(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazole (DAMNI) analogs by Glide v5.0 and Scigress Explorer Ultra 7.7 respectively and to predict the suitable binding modes of the DAMNI analogs in the hydrophobic binding pockets of NNIBP.

EXPERIMENTAL

Docking studies were performed on DAMNI analogs 1-68[18-20] by using both Glide 5.0[21] and BioApplications Module of Scigress Explorer Ultra 7.7 [22]software.

Computational methods with Glide5.0

All computational studies were carried out using Glide version 5.0. installed in a single machine running on a 3.4 GHz Pentium 4 processor with 1GB RAM and 160 GB Hard Disk with Red Hat Linux Enterprise version 5.0 as the Operating System.

Protein structure preparation in Glide5.0

Protein Preparation Wizard of Schrodinger Inc., has been used to prepare protein. The geometry of the NNBS of the wt RT strain was taken from the structure of HIV-1 RT/TNK 651 complex filed in the Brookhaven Protein Data Bank[23] (entry code 1rt2). Water and chain-B were deleted. After assigning charge and protonation state finally energy minimization was done using OPLS2005 force field.

Validation of the docking protocol in Glide

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. In the present study, the docking of TNK 651 which is extracted previously from 1rt2 receptor complex into the RT was performed to test the reliability and reproducibility of the docking protocol for our study. We found a very good agreement between the localization of the inhibitor TNK 651 upon docking and from the crystal structure (Fig. 1). The root mean square deviations (RMSD) between the predicted conformation and the observed X-ray crystallographic conformation of compound TNK 651 equaled 2.445 Å by Glide (3 Å). This indicates the reliability of the docking method in reproducing the experimentally observed binding mode for HIV-1 RT.

Ligand structure preparation in Glide

Ligand structures were drawn and optimized using PRODRG online server[24] and saved in PDB format. By using the Ligprep utility of Glide, these structures were geometry optimized by using the Optimized Potentials for Liquid Simulations-2005 (OPLS-2005) force field with the steepest descent followed by truncated Newton conjugate gradient protocol. Partial atomic charges were computed using the OPLS-2005 force field.

Molecular docking protocol

All docking calculations were performed using the "Extra Precision" (XP) mode of Glide Program 5.0. A grid was prepared with the center defined by the co-crystallized ligand TNK 651 of 1rt2. During the docking process, initially Glide performs a complete systematic search of the conformational, orientational and positional space of the docked ligand and eliminating unwanted conformations using scoring and followed by energy optimization. Finally the conformations are further refined via Monte Carlo sampling of pose conformation. Predicting the binding affinity and rank-ordering ligands in database screens was implemented by modified and expanded version of the Glide Score scoring function.

Docking of the ligands in Glide

After the validation of the both docking methods using TNK 651, all the DAMNI analogs 1 to 68 were docked into the same coordinates of the crystal structure. The docked 3D-structures of 1-{2-(diarylmethoxy) ethyl]-2-methyl-5-nitroimidazole (DAMNI) derivatives were scored.

Computational methods with Scigress Explorer Ultra 7.7:

All computational studies were carried out using Scigress Explorer 7.7 installed in a single machine running on a 3.4 GHz Intel Core 2 Duo Processor with 1GB RAM and 160 GB Hard Disk with Windows XP as the Operating System.

Ligand structure preparation

Ligand structures were drawn on Scigress Explorer user interface which provides advanced visualization, analysis and drawing tools. The ligands were stored in .csf format. These structures were geometry optimized by using the MM3 force-field runs.

Protein structure preparation

The geometry of the NNBS of the wt RT strain was taken from the structure of HIV-1 RT/TNK 651 complex filed in the Brookhaven Protein Data Bank[23] (entry code 1rt2). Water and chain-B were deleted. After assigning charge and protonation state finally refinement (energy minimization) was done using MM3 force field runs.

Validation of the docking protocol

The docking of TNK 651 into 1rt2 RT receptor complex was performed to test the reliability and reproducibility of the docking protocol for our study (Fig.2). The root mean square deviations (RMSD) between the predicted conformation and the observed X-ray crystallographic conformation of compound TNK 651 equaled 1.06 Å. This indicates the reliability of the docking method in reproducing the experimentally observed binding mode for HIV-1 RT.

Automatic Docking and Scoring

All ligands 1 to 68 were docked into the active site of the crystal structure of RT (PDB entry code 1rt2) using automated docking. The docked 3D-structures of 1-{2-(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazole (DAMNI) derivatives were scored .

RESULTS AND DISCUSSION

To investigate the detailed intermolecular interactions between the ligand and the target protein, two different types of automated docking programs Glide 5.0 and Scigress Explorer Ultra 7.7 were used. The docking scores are summarized in Table 1.

Docking with Glide version 5.0:-

All the 68 DAMNI analogs[18-20] were docked in the NNIBP of RT (PDB entry code 1rt2) using Glide version 5.0. In case of all the DAMNI analogs both R and S configurations produce almost the same binding energies. Fig. 3 and Fig. 4 map the binding mode of highest experimentally active compound 31 (dock score of 12.18) and the compound 23 with lowest binding energy of 13.44 in glide to the active site of RT receptor (PDB entry 1rt2) respectively.

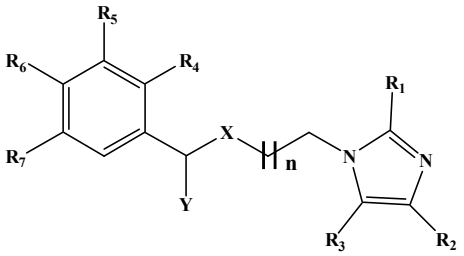
As depicted in the Fig.3, the phenyl ring of the compound 31 is placed in the hydrophobic pocket formed by TYR181, TYR188, PRO95, PHE227, TRP229 and LEU234. Similar orientation was found in case of compound 23 (Fig.4). The thiophene ring is in the pocket formed by the amino acids VAL189, VAL179, GLY190, LEU100, VAL106 and ILEU180. The side chain ethyl bridge makes favourable interactions with VAL106. Both the molecules also form strong H-bonds with amino acid LYS103. The distance between the 'N' of imidazole and LYS103 is calculated as 2.914Å for compound 31 and 2.039 Å for compound 23.A correlation was calculated between Glide score and the pEC50 values via a linear regression analysis. A correlation coefficient 0.24718 r and 0.061 r^2 between experimental pEC50 and XP docking scores (Fig.5) was obtained.

***Docking with Scigress Explorer Ultra 7.7*:**

All the 68 DAMNI analogs[18-20] were docked in the NNIBP of RT (PDB entry code 1RT2) by using Scigress Explorer Ultra 7.7 for comparison purposes. Compound 31, the highest experimentally active molecule was found to have a docking score of -111.361 (Fig.6), while compound 9 had the highest docking score of -116.210 (Fig.7). A closer investigation of the binding mode of the compound 9 revealed that one phenyl group occupies a more lipophillic pocket formed by the side chains of TYR181, TYR 188, PHE 227 and TRP 229. The other phenyl ring occupies the milder hydrophobic pocket LEU 100, VAL 106, VAL 179 and GLY190. The 2-methyl 5-nitroimidazolyl moiety was oriented towards the least hydrophobic portion of NNBS, formed by the side chains of PRO 225, HIS 235, PRO 236 and LEU 234. Similar orientation was obtained for the compound 31 both for the R and the S configurations. It was interesting to note that the compounds 6,7,18, 20, 26, 63, 65 and 66 all provided positive docking scores. This could be explained by the fact that compounds 6 and 7 had bulky groups in the *para* position of the second phenyl group and these groups were blocking the entry of the compound into the NNBS cavity. Similarly, the compounds 17, 20 and 26 contained bulky groups at 5, 6 and 7 positions of the first phenyl group respectively which was presumably causing the same kind of steric hindrance. The fact that the methyl group was crucial for activity was evident from the positive scores obtained for compounds 65 and 66 which were devoid of the methyl group at the 2 position of the imidazole nucleus. The docking scores are summarized in Table 4. A correlation was also calculated between the docking scores and the pEC50 values via a linear regression analysis. A better correlation coefficient of 0.8761 r and 0.7675 r^2 between experimental pEC50 and docking scores (Fig.8) was obtained with Scigress Explorer. However, the compounds 6,7,18, 20, 26, 63, 65 and 66 which generated positive scores were left out while carrying out the correlation analysis.

From the above studies, it is concluded that the DAMNI analogs bind by a butterfly like conformation in the NNIBP pocket of reverse transcriptase. The essential requirements for binding of the DAMNI analogs to the NNIBP are the imidazolyl group with the CH_2CH_2O side chain as the hydrophilic group surrounded by two aryl hydrophobic moieties, one of which is to be substituted with smaller hydrophobic groups (Fig.9). The methyl and the nitro group at the 2^{nd} and 5^{th} position of the imidazole nucleus are crucial for NNRTI activity of the DAMNI analogs. Results of this study may be utilized for future drug design studies and synthesis of more potent DAMNI analogs as HIV-1 RT inhibitors. It is also evident that in comparison to Glide, better correlation results are achieved with docking using the BioApplications Module of Scigress Explorer Ultra, thus suggesting that Scigress Explorer is an effective desktop modelling tool in virtual screening and *in silico* design and optimization of lead molecules for NNRTI activity.

Table 1. Glide XP scores and Scigress scores of DAMNI analogs 1to 68 docked to the NNIBP of HIV-1 RT (1rt2)



Compd	X	Y	n	R1	R2	R3	R4	R5	R6	R7	Binding free energy (kcal/mole)		pEC_{50}
											Glide XP scores	Scigress scores	
1	O	C_6H_5	1	H	H	H	H	H	H	H	-11.34	-106.103	2
2	O	C6H5	1	H	H	H	Cl	Cl	H	H	-12.13	-73.767	1.49
3	O	C_6H_4 Cl	1	H	H	H	Cl	Cl	H	H	-10.50	-82.554	1.41
4	O	C_6H_5	1	CH_3	H	NO_2	H	H	H	H	-12.46	-109.177	0.69
5	O	C_6H_4 CH_3	1	CH_3	H	NO_2	H	H	H	H	-12.13	-94.486	0.146
6	O	*p*-tert-Bu - C_6H_4	1	CH_3	H	NO_2	H	H	H	H	-11.21	Positive	0.60
7	O	*p*-C_6H_6-C_6H_4	1	CH_3	H	NO_2	H	H	H	H	-11.14	Positive	1.23
8	O	*p*-F C_6H_4	1	CH_3	H	NO_2	H	H	H	H	-12.99	-93.905	0.045
9	O	*p*-ClC_6H_4	1	CH_3	H	NO_2	H	H	H	H	-12.51	-116.210	1.096
10	O	C_6H_5	1	CH_3	H	NO_2	Cl	Cl	H	H	-7.00	-99.332	0.176
11	O	C_6H_5	1	CH_3	H	NO_2	CH_3	H	H	H	-12.44	-93.863	0.69
12	O	C_6H_5	1	CH_3	H	NO_2	F	H	H	H	-13.03	-108.714	0.069
13	O	C_6H_5	1	CH_3	H	NO_2	Cl	H	H	H	-12.28	-69.857	0.22
14	O	C_6H_5	1	CH_3	H	NO_2	H	CH_3	H	H	-12.50	-94.587	1
15	O	C_6H_5	1	CH_3	H	NO_2	H	F	H	H	-13.18	-100.081	1
16	O	C_6H_5	1	CH_3	H	NO_2	H	Cl	H	H	-12.34	-98.059	0.69
17	O	C_6H_5	1	CH_3	H	NO_2	H	NO_2	H	H	-12.29	-96.746	0.22
18	O	C_6H_5	1	CH_3	H	NO_2	H	1-pyr olyl	H	H	-12.53	Positive	1.146
19	O	C_6H_5	1	CH_3	H	NO_2	H	H	NO_2	H	-12.39	-46.620	0.69
20	O	C_6H_5	1	CH_3	H	NO_2	H	H	NHC OCH_3	H	-12.12	Positive	2.3
21	O	C_6H_5	1	CH_3	H	NO_2	H	H	OCH_3	H	-12.65	-67.184	1.93
22	O	C_6H_5	1	CH_3	H	NO_2	H	CH_3	H	CH_3	-12.43	-65.324	0.39
23	O	C_6H_5	1	CH_3	H	NO_2	H	F	H	F	-13.44	-97.927	0

24	O	C_6H_5	1	CH_3	H	NO_2	H	Cl	H	Cl	-12.41	-107.447	1.65
25	O	C_6H_5	1	CH_3	H	NO_2	H	Cl	Cl	H	-12.36	-92.975	1.98
26	O	C_6H_5	1	CH_3	H	NO_2	H	H	H	CH=CH-CH=CH$_2$	-12.49	Positive	2.025
27	O	C_6H_5	2	CH_3	H	NO_2	H	H	H	H	-12.25	-55.929	1.544
28	O	C_6H_5	1	CH_3	H	NO_2	H	H	CH_3	H	-12.54	-49.106	0.761
29	O	C_6H_5	1	CH_3	H	NO_2	H	H	F	H	-13.28	-109.931	0.781
30	O	C_6H_5	1	CH_3	H	NO_2	H	H	Cl	H	-12.48	-107.339	0.69
31	O	thiophen-	1	CH_3	H	NO_2	H	H	H	H	-12.18	-111.361	1.522
32	O	thiophen-	1	CH_3	H	NO_2	CH_3	H	H	H	-12.50	-97.168	0.346
33	O	thiophen-	1	CH_3	H	NO_2	H	H	CH_3	H	-12.44	-90.145	0.522
34	O	thiophen-	1	CH_3	H	NO_2	Cl	H	H	H	-12.39	-94.861	0.278
35	O	thiophen-	1	CH_3	H	NO_2	H	Cl	H	H	-12.36	-82.991	1.096
36	O	thiophen-	1	CH_3	H	NO_2	H	H	Cl	H	-12.36	-113.488	1.76
37	O	thiophen-	1	CH_3	H	NO_2	F	H	H	H	-12.87	-102.617	0.92
38	O	thiophen-	1	CH_3	H	NO_2	H	F	H	H	-12.86	-103.217	0.85
39	O	thiophen-	1	CH_3	H	NO_2	H	H	F	H	-12.43	-108.141	0.49
40	O	thiophen-	1	CH_3	H	NO_2	F	F	H	H	-13.22	-104.166	1.22
41	O	5-chloro-thiophen	1	CH_3	H	NO_2	H	H	H	H	-12.63	-105.419	0.079
42	O	oxazolo	1	CH_3	H	NO_2	H	H	H	H	-12.50	-104.203	1
43	O	3-pyridine	1	CH_3	H	NO_2	H	H	H	H	-12.69	-107.183	1.096
44	S	C_6H_5	1	CH_3	H	NO_2	H	H	H	H	-12.43	-115.263	-0.0079
45	S	C_6H_5	1	CH_3	H	NO_2	Cl	H	H	H	-12.46	-106.431	1.079
46	S	C_6H_5	1	CH_3	H	NO_2	F	H	H	H	-12.93	-89.764	0.698
47	S	C_6H_5	1	CH_3	H	NO_2	H	CH_3	H	H	-12.68	-66.725	0.477
48	S	C_6H_5	1	CH_3	H	NO_2	H	Cl	H	H	-12.29	-102.361	1.80
49	S	C_6H_5	1	CH_3	H	NO_2	H	F	H	H	-13.43	-89.705	1.90
50	SO_2	C_6H_5	1	CH_3	H	NO_2	H	H	H	H	-11.65	-67.507	0.716
51	S	H	1	CH_3	H	NO_2	H	H	H	H	-10.35	-98.283	1.77
52	NH	C_6H_5	1	CH_3	H	NO_2	H	H	H	H	-7.88	-99.29	1.079
53	NH	C_6H_5	1	CH_3	H	NO_2	Cl	H	H	H	-5.95	-96.104	1.27
54	NH	C_6H_5	1	CH_3	H	NO_2	F	H	H	H	-8.96	-97.155	1.69
55	NH	C_6H_5	1	CH_3	H	NO_2	H	CH_3	H	H	-9.59	-80.673	1.81

56	NH	C_6H_5	1	CH_3	H	NO_2	H	Cl	H	H	-8.23	-103.167	0.322
57	NH	C_6H_5	1	CH_3	H	NO_2	H	F	H	H	-9.08	-96.870	0.255
58	NH	C_6H_5	1	CH_3	H	NO_2	H	H	CH_3	H	-7.57	-45.033	1.64
59	NH	C_6H_5	1	CH_3	H	NO_2	H	H	F	H	-9.19	-78.054	1.96
60	NH	H	1	CH_3	H	NO_2	H	H	H	H	-5.86	-84.805	2
61	N-benzyl	H	1	CH_3	H	NO_2	H	H	H	H	-11.34	-92.181	1.924
62	O	C_6H_5	1	CH_3	NO_2	H	H	H	H	H	-12.13	-110.826	1.82
63	O	2-napthyl	1	CH_3	H	NO_2	H	H	H	H	-10.50	Positive	2
64	O	cyclohexyl	1	CH_3	H	NO_2	H	H	H	H	-12.46	-67.268	0.522
65	O	C_6H_5	1	H	H	NO_2	H	H	H	H	-12.13	Positive	2
66	O	C_6H_5	1	H	NO_2	H	H	H	H	H	-11.21	Positive	1.89
67	O	H	1	CH_3	H	NO_2	H	H	H	H	-11.14	-96.371	0.62
68	O	H	1	CH_3	NO_2	H	H	H	H	H	-12.99	-108.073	1.32

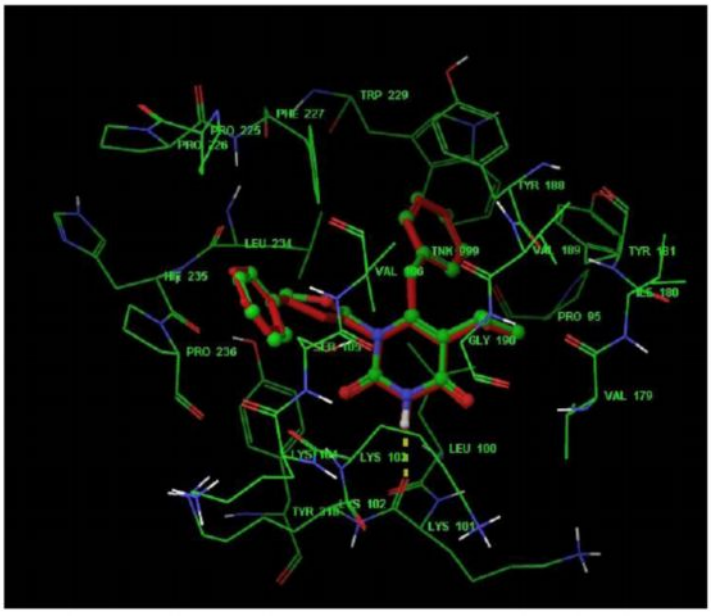


Fig.1: Validation of docking by Glide. Superimposition of experimental bound (cocrystallized) conformation of TNK651 (red) and that predicted by Glide (green) (ball and stick model). Active site amino acid residues are represented as sticks.

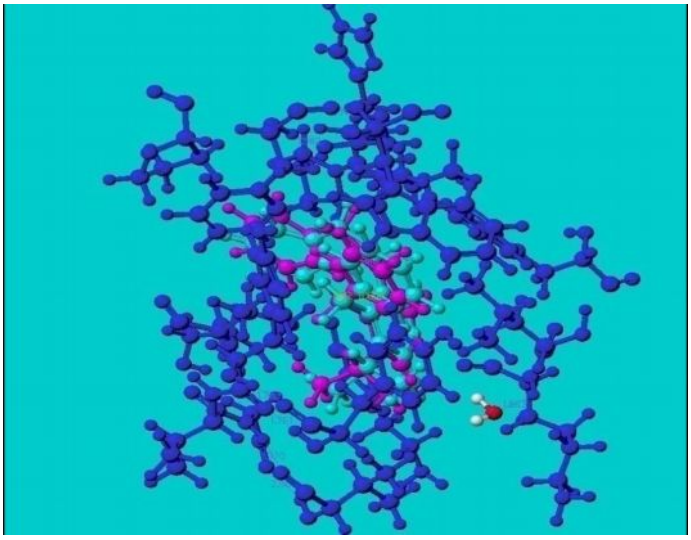


Fig.2: Validation of PMF method. Superimposition of experimental bound conformation of TNK 651 (magenta) and redocked conformer (cyan) (ball and stick model). Active site amino acid residues are represented in blue.

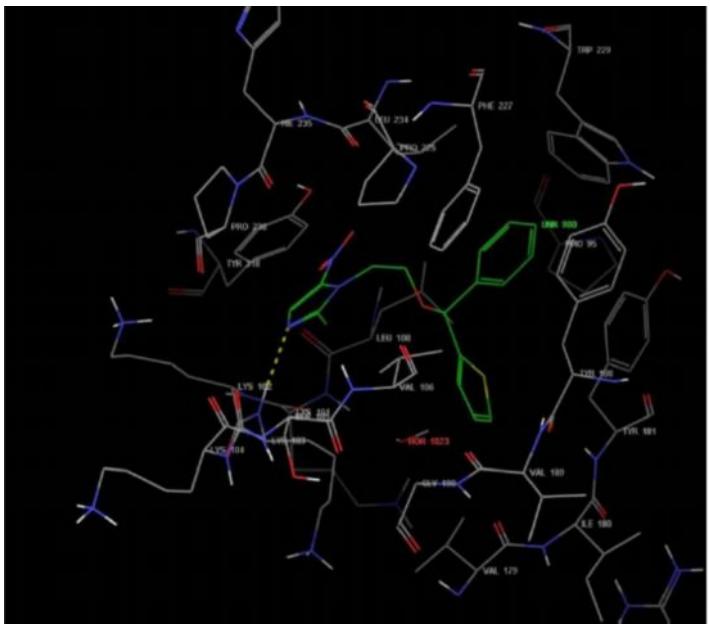


Fig.3: XP Glide-predicted pose of highly active molecule 31 with dock score (-12.182). Active site amino acid residues and inhibitor are represented as sticks. Inhibitor 22a is colored with the atoms as carbon: green, hydrogen: cyan, nitrogen: blue, and oxygen: red.

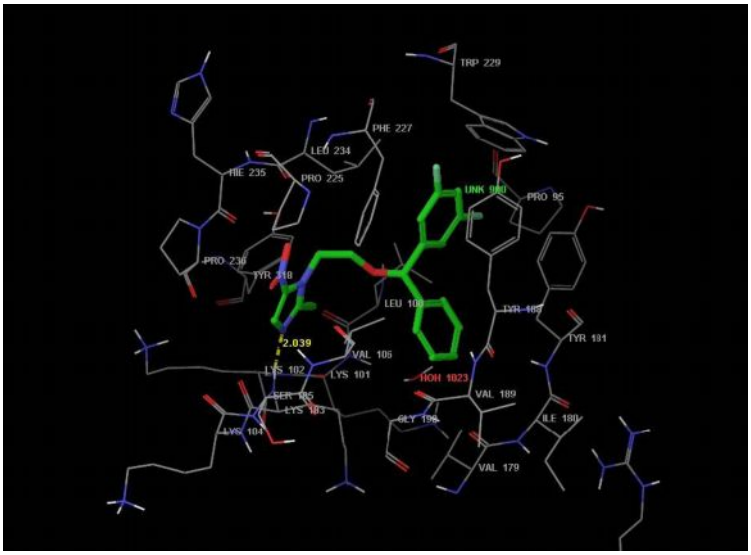


Fig.4: XP Glide-predicted pose of lowest binding energy molecule 23 with dock score (-13.144). Active site amino acid residues are represented as sticks while the inhibitor is shown as tube model with the atoms colored as carbon: green, hydrogen: cyan, nitrogen: blue, and oxygen: red.

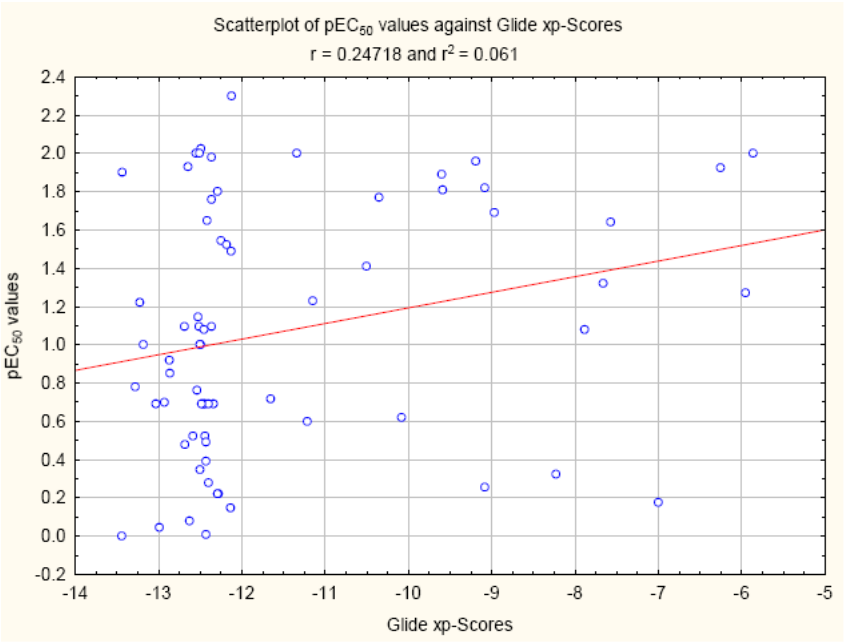


Fig.5: Scatterplot of Glide XP docking scores of the DAMNI analogs 1-68 vs pEC_{50}.

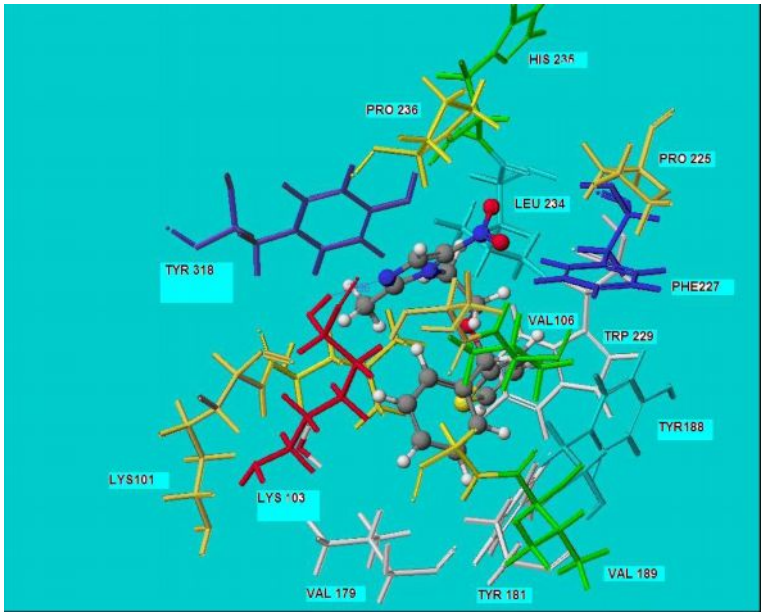


Fig.6: Cache Scigress Explorer predicted pose of highest experimentally active molecule 31 with score (-111.361). Active site amino acid residues are represented as sticks colored according to residue type (Sequence protocol-Karplus and Schultz Flexibility). Molecule 22a is colored with the atoms as carbon: grey, hydrogen: white, nitrogen: blue, and oxygen: red (ball and stick model).

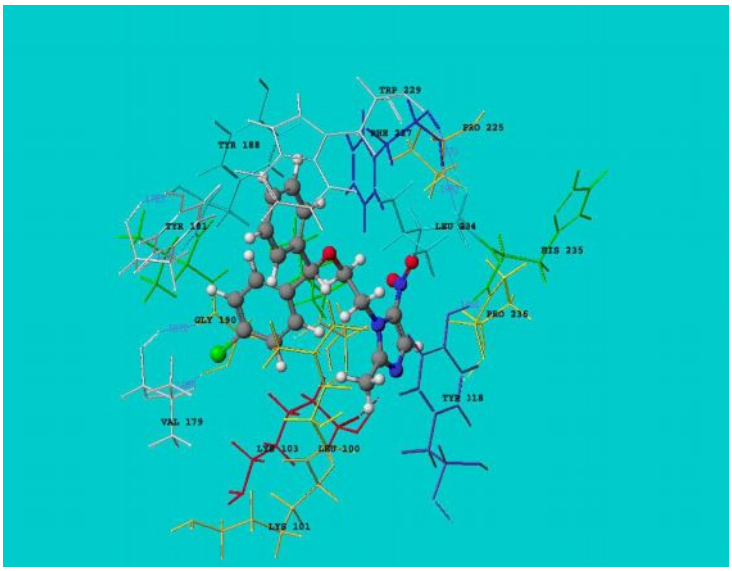


Fig.7: Cache Scigress Explorer predicted pose of molecule 9 with highest dock score (-116.21). Active site amino acid residues are represented as sticks colored according to residue type (Sequence protocol-Karplus and Schultz Flexibility). Molecule 20i is colored with the atoms as carbon: grey, hydrogen: white, nitrogen: blue, and oxygen: red (ball and stick model).

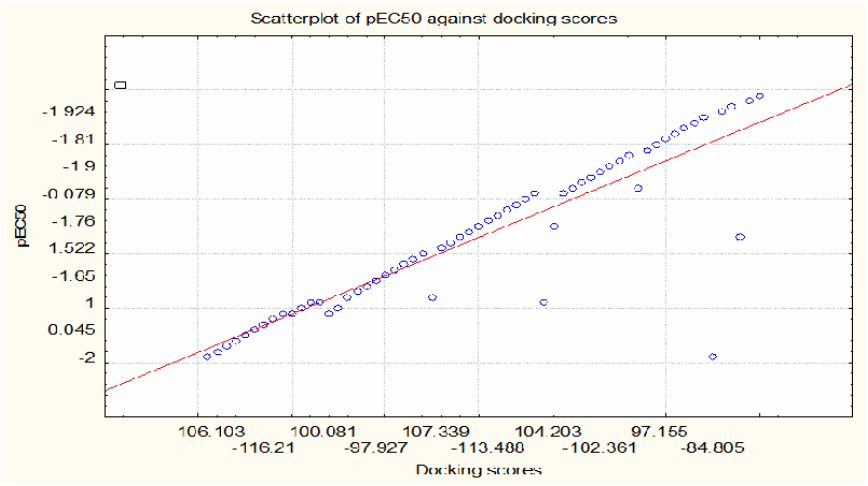


Fig.8: Scatterplot of Scigress docking scores of the DAMNI analogs 1-68 vs pEC_{50}.

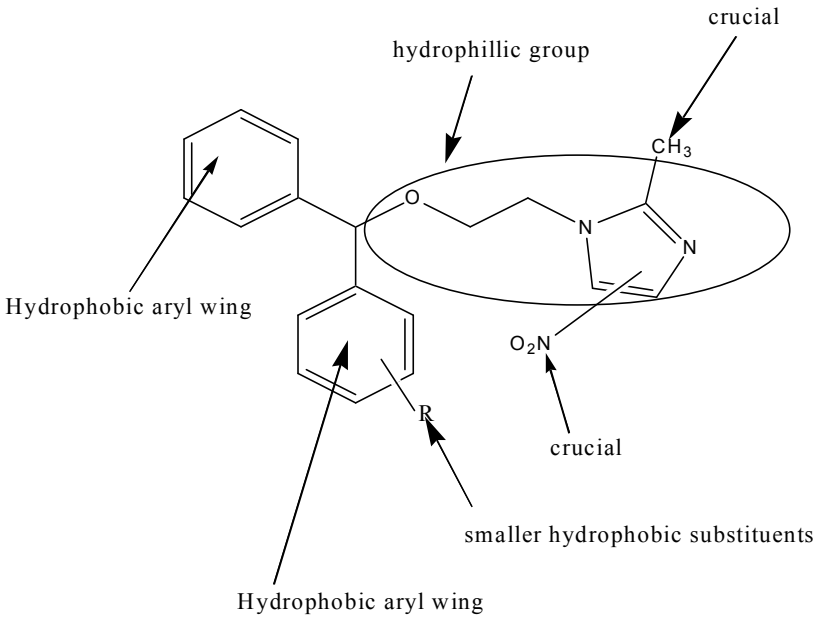


Fig. 9. : Groups required for HIV-1-RT inhibitory activity.

REFERENCES

1. Das K., Lewi P. J., Hughes S.H and Arnold E., Crystallography and the design of anti AIDS drugs: conformational flexibility and positional adaptability are important in design of non nucleoside HIV-1- reverse transcriptase inhibitors, Prog. Biophy. Mol. Biol., 2005, 88, 209-231.

2. Freitas R. F. and Galembeck S. E., Computational study of the interaction between TIBO inhibitors and Y181 (C181), K101, and Y188 amino acids, J. Phys .Chem B., 2006, 110(42), 21287-98.

3. Bell F. W., Cantrell A. S., Hoegberg M., Jaskunas S. R., Johansson N. G., Jordan C. L., Kinnick M. D., Lind P. and Morin Jr. J. M., Phenethylthiazolethiourea (PETT) Compounds, a New Class of HIV-1 Reverse Transcriptase Inhibitors. 1. Synthesis and Basic Structure-Activity Relationship Studies of PETT Analogs, J. Med. Chem., 1995, 38 (25), 4929–4936.

4. Sriram D., Bal T. R. and Perumal Y., Design, synthesis and biological evaluation of novel non-nucleoside HIV-1 reverse transcriptase inhibitors with broad-spectrum chemotherapeutic properties, Bioorganic & Medicinal Chemistry 2004,12 , 5865–5873.

5. Koska J., Spassov V. Z., Maynard A. J., Yan L., Austin N., Flook P. K. and Venkatachalam C. M. Fully Automated Molecular Mechanics Based Induced Fit Protein-Ligand Docking Method, J. Chem. Inf. Model., 2008, 48, 1965–1973.
6. Yusuf D.; Davis A. M.; Kleywegt G. J. and Schmitt, S. An Alternative Method for the Evaluation of Docking Performance: RSR vs RMSD, J. Chem. Inf. Model., 2008, 48, 1411–1422.
7. Krovat E. M., Steindl T. and Langer T., Recent Advances in Docking and Scoring, Current Computer-Aided Drug Design, 2005, 1, 93-102
8. Delgado J. N. and Remers W. A., Antiprotozoal Agents: Wilson and Gisvold's Text book of Organic Medicinal and Pharmaceutical Chemistry, 10th ed; Lippincott-Raven Publishers: New York, 1998, 210.
9. Hoffer M. and Grunberg E., Synthesis and antiprotozoal activity of 1-(3-chloro-2-hydroxypropyl)-substituted nitroimidazoles, *J. Med. Chem.,* **1974**, 17 (9), 1019–1020.
10. Mrocz Kioenicz A.; Acta. Pol. Pharm., 1981. 38(5), 555 through Chem. Abstr., 1982. 97, 722-787.
11. Nasvadba N., Hellmuth, H. and Offen, G. 1976, 2, 553 through Chem. Abstr. 1976, 85, 123-124.
12. Raether, W. and Hanel H. Nitroheterocyclic drugs with broad spectrum activity, Parasitol Res., 2003, 90, S19–S39.
13. Tweit R. C., Muir R. D. and Ziecina S., Nitroimidazoles with antibacterial activity against *Neisseria gonorrhoeae*, J. Med. Chem. 1977, 20(12), 1697-1700.
14. Coffey S. and Ansell, M. F., Heterocyclic compounds: Rodd's Chemistry of Carbon Compounds, 4th ed, Elsevier Science: New York, 1986, 139-147.
15. Winkelmann E., Raether W. and Sinharay A., Chemotherapeutically Active Nitro Compounds. 4. 5-Nitroimidazoles. Part I, Arzneim. -Forsch., 1977, 27(12), 2251-2263.
16. Miller, M. W., Howes, H. L, Kasubick, R. V. and English, A. R. Alkylation of 2-methyl-5-nitroimidazole. Some potent antiprotozoal agents, J.Med.Chem., 1970, 13(5), 849-852.
17. Ganguly S.,Singh S.P and Chandra R., Synthesis and Antimicrobial Activity of some new 2-methyl-5-nitroimidazole derivatives, Jr. Ind. Chem. Soc., 2004, 81, 781-782
18. Silvestri R., Artico, M., Massa, S, Marceddu, T., De Montis, F. and La Colla, P. 1-[2-(Diphenylmethoxy) ethyl]-2-methyl-5-nitroimidazole: a Potent Lead for the Design of Novel NNRTIs, Bioorg. Med.Chem. Lett., 2000, 10, 253-256.
19. Silvestri, R., Artico, M., Demartino, G., Ragno, R., Massa, S., Lodda, R., Mugioni, C., Giulia loi, A., La Colla, P. and Pani, A. Synthesis, Biological Evaluation and Binding Mode of Novel 1-[2-(Diarylmethoxy) ethyl]-2-methyl-5-nitroimidazoles targeted at the HIV-1 Reverse Transcriptase, J.Med.Chem., 2002, 45, 1567-1576.
20. De martino, G., Regina, G., Di pasquali, A., Bergamini, A., Ciaprini, C., Sinistro, A., Maga, G., Crespan, E., Artico, M. and Silvestri, R., Novel 1-[2-(Diarylmethoxy) ethyl]-2-methyl-5-nitroimidazoles as HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors. A Structure-Activity Relationship Investigation, J. Med. Chem., 2005, 48, 4378-4388.
21. Glide 5.0 User Manual, Schrödinger, Inc. New York, U.S.A , 2008.
22. Scigress Explorer Ultra 7.7 Bio Applications Getting Started Manual, Fujitsu Limited, Poland, 2008.
23. www.rcsb.org
24. http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg/prodrg.cgi

*****