Available online at www.scholarsresearchlibrary.com

Scholars Research Library

***J. Comput. Method. Mol. Design*, 2011, 1 (3): 39-48**
(http://scholarsresearchlibrary.com/archive.html)

ISSN : 2231- 3176
CODEN (USA): JCMMDA

Exploring interactions of 2-Amino-6-arylsulfonylbenzonitrile derivatives as non-nucleoside reverse transcriptase inhibitors of HIV-1 using docking studies

Vijay H. Masand[a]*, Komalsingh N. Patil[a], Rahul D. Jawarkar[b], Taibi Ben Hadda[c*], Moulay Hfid Youssoufi [c], Ahmed A. Alafeefy[d]

[a] *Department of Chemistry, Vidya Bharati College, Camp, Amravati, Maharashtra, India-444602*
[b] *Department of Pharmaceutical Chemistry, Sahyadri college of pharmacy, Methwade, Sangola, Solapur Maharashtra, India*
[c] *Laboratoire Chimie des Matériaux, Université Mohammed Premier, Oujda, Morocco.*
[d] *Department of Pharmaceutical Chemistry, College of Pharmacy, Alkharj University, Alkharj, 11451, P.O. Box 2457, Saudi Arabia*

ABSTRACT

We report docking studies of 2-Amino-6-arylsulfonylbenzonitrile derivatives as non-nucleoside HIV-1 reverse transcriptase inhibitors. Docking studies were performed on three different types of 2-Amino-6-arylsulfonylbenzonitrile derivatives to focus on the application of docking methods and parameters to study substrate–enzyme interactions of 2-Amino-6-arylsulfonylbenzonitrile derivatives as ligand with immunodeficiency virus reverse transcriptase as receptor. In present study structure-based drug design flexible docking were performed to get better understanding of binding mode of ligand with receptor. Docking studies explores different substituents as well as hydrophobic, steric and electronic features which affects and are essential for non-nucleoside RT inhibitors to show anti-HIV-1 activity. The present analysis reveals that presence of cyano group on aromatic ring and –Cl at position 3 are positive factors for anti-HIV activity.

Keywords: computer-aided drug design, human immunodeficiency virus reverse transcriptase, structure-based drug design, 2-Amino-6-arylsulfonylbenzonitrile derivatives

---

INTRODUCTION

Acquired immuno deficiency syndrome (AIDS), caused by the HIV virus, is one of the world's pandemic disease with crucial medical, economic and social impact on the modern world. The current chemotherapy, combining three or more drugs, is increasing the survival of HIV-infected patients for longer time and provides an improved quality of life. But due to increasing emergence of drug resistance Highly Active Antiretroviral Therapy (HAART) has received a setback. Therefore, the issue of rapid emergence of resistance virus has to be tackled by designing either new potent efficient inhibitors or by modifying the existing drugs in order to inhibit wild type HIV-1 as well as pre-existing resistant viral variants due to occurrence of

mutations during ongoing viral replication. Computer-aided drug design designing is a powerful tool for designing new drug or modifying existing drug. These methods are simple, non-expensive and accelerate the process of designing novel and potent molecules with desired biological activity [1-7].

Quantitative structure activity relationship (QSAR) and docking methods are two generally used computational methods in structure-based drug design (SBDD). In QSAR methodologies, a mathematical relationship, relating the biological activity to some molecular descriptors is obtained. In docking studies, different search algorithms such as simulated annealing and genetic algorithm in combination with scoring function such as molecular mechanic calculations are being used to study the binding of the ligands to a protein with known structure. Thus docking is an attempt to predict the structure of the intermolecular complex formed between two or more constituent molecules. Through docking procedures, not only new biological active compound is introduced, but also the chemistry of the ligand–protein interaction is well recognized.

The current therapies for HIV inhibition are chiefly based on the inhibition of three key viral enzymes: HIV-1 reverse transcriptase (RT), HIV-1 protease and HIV-1 integrase. The inhibition of RT is considered as one of the most attractive targets in the anti-HIV chemotherapy because it does not exist in Humans and play important role in the viral replication. Based on the chemical structures and the inhibitory mechanism, the RT inhibitors are classified as nucleoside and nucleotide RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs). NRTIs binds to the active site of RT and act as substrate decoys and chain terminators whereas NNRTIs bind to an allosteric site of HIV-1 RT located about 10 Å away from the catalytic site [8],[9].

The NNRTIs play an important role in current anti-HIV therapy as a part of a successful combination therapy due to safety, selectivity and high potency. Different aspects of NNRTIs have recently been reviewed [10], [11]. In present work we have used flexible docking to explore the binding of 2-Amino-6-arylsulfonylbenzonitrile derivatives which are NNRTIs with HIV-1 RT. Use of flexible docking can enhance the drug design process by making it more reasonable [12], and the inclusion of that flexibility could be decisive when targeting a highly dynamic protein, such as HIV-1 RT. X-ray crystallographic studies shows that RT is a 1000-amino-acid heterodimer of p66 and p51 subunits, which are each composed of “fingers,” “thumb,” “palm” and “connection sub domains [13]. Considering the huge conformational changes associated as well as the large size and the extensive flexibility displayed by the HIV-1 RT inhibitors that are currently used clinically, applying the flexible docking will be useful to understand the types of interactions between these NNRTIs and HIV-1 RT.

MATEIALS AND MEHTODS

2. Experimental protocol / Computational approach

2.1 Data set:

2-Amino-6-arylsulfonylbenzonitrile derivatives developed by Chan [14] along with their biological activities are taken for docking studies and are listed in table 1 along with their biological activities, expressed in terms of pIC_{50}. The compounds include structurally diverse derivatives of 2-Amino-6-arylsulfonylbenzonitrile with substituents like -Cl, $-CH_3$ etc. Only those derivatives are considered here for which accurate value of pIC_{50} was reported.

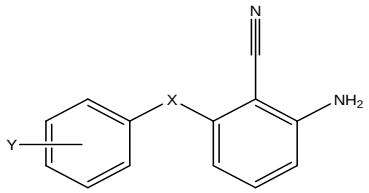

Figure 1: structure of 2-Amino-6-arylsulfonylbenzonitrile derivatives

Table1. Anti-HIV-1 activity (inhibitory concentration pIC_{50}) of 2-Amino-6-arylsulfonylbenzonitrile derivatives

Sr. No.	*Code*	*X*	*Y*	IC_{50}	pIC_{50}
1	S1	S	3-Cl	16.000	-1.2041
2	S2	S	3,5-Cl_2	0.120	0.9208
3	S3	S	2 –OCH_3	2.700	-0.4314
4	S4	S	3–OCH_3	1.500	-0.1761
5	S5	S	3–CH_3	0.960	0.0177
6	S6	S	4-–CH_3	5.700	-0.7559
7	S7	S	2- Cl	7.200	-0.8573
8	S8	S	4-Cl	12.000	-1.0792
9	S9	S	3-Br	15.000	-1.1761
10	S10	S	3-F	12.000	-1.0792
11	S11	S	2-CN	9.100	-0.9590
12	S12	S	3-CN	1.100	-0.0414
13	S13	S	3-CF_3	7.100	-0.8513
14	S14	S	2,5-Cl_2	3.500	-0.5441
15	S15	S	3,5-$(CH_3)_2$	1.100	-0.0414
16	S16	S	3-Cl, 5-CH_3	1.700	-0.2304
17	S17	S	3–OCH_3, 5 –CH_3	0.140	0.8539
18	S18	S	3–OCH_3, 5 –CF_3	13.000	-1.1139
19	S19	S	H	8.700	-0.9395
20	SO1	SO	3-OCH_3	19.000	-1.2788
21	SO2	SO	3,5-$(CH_3)_2$	0.500	0.3010
22	SO3	SO	2–OCH_3	12.000	-1.0792
23	SO4	SO	3–CH_3	10.000	-1.0000
24	SO5	SO	3-Br	4.800	-0.6812
25	SO6	SO	2-CN	9.900	-0.9956
26	SO7	SO	2,5-Cl_2	6.200	-0.7924
27	SO8	SO	3-Cl, 5–CH_3	0.520	0.2840
28	SO9	SO	3–OCH_3, 5 –CF_3	0.900	0.0458
29	OSO1	SO_2	4-OCH_3	13.000	-1.1139
30	OSO2	SO_2	3-Br, 5-CH_3	0.003	2.5229
31	OSO3	SO_2	H	6.900	-0.8388
32	OSO4	SO_2	2–OCH_3	1.400	-0.1461
33	OSO5	SO_2	3-OCH_3	0.600	0.2218
34	OSO6	SO_2	2-CH_3	4.500	-0.6532
35	OSO7	SO_2	3-CH_3	0.200	0.6990
36	OSO8	SO_2	4-CH_3	7.300	-0.8633
37	OSO9	SO_2	2-Cl	5.900	-0.7709
38	OSO10	SO_2	3-Cl	0.400	0.3979
39	OSO11	SO_2	2-Br	12.000	-1.0792
40	OSO12	SO_2	3-Br	0.200	0.6990
41	OSO13	SO_2	2-F	5.000	-0.6990
42	OSO14	SO_2	2-CN	6.000	-0.7782
43	OSO15	SO_2	3-CN	1.800	-0.2553
44	OSO16	SO_2	3–CF_3	5.300	-0.7243
45	OSO17	SO_2	2,5-Cl_2	0.300	0.5229
46	OSO18	SO_2	3,5-Cl_2	0.030	1.5229
47	OSO19	SO_2	3,5-$(CH_3)_2$	0.010	2.1549
48	OSO20	SO_2	3-Cl, 5–CH_3	0.010	2.3010
49	OSO21	SO_2	3–OCH_3, 5 –CH_3	0.010	2.0000
50	OSO22	SO_2	3–OCH_3, 5 –CF_3	0.040	1.3979
51	OSO23	SO_2	3-$O(CH_2)_3$-CH_3, 5-CH_3	0.400	0.3979
52	OSO24	SO_2	1-naphthyl	1.000	0.0000
53	OSO25	SO_2	2-naphthyl	0.030	1.5229

3. Computational methods

3.1 Molecular structures

The molecular structures were drawn and optimized using ChemDraw ultra 11.0 and exported to Molecular Operating Environment (MOE). MOE-Dock utilizes a Monte Carlo simulated annealing process for docking a substrate into the active site of a macromolecule. The molecular structures were further prepared along with the proteins (charges and protonation states were assigned) by the docking engine.

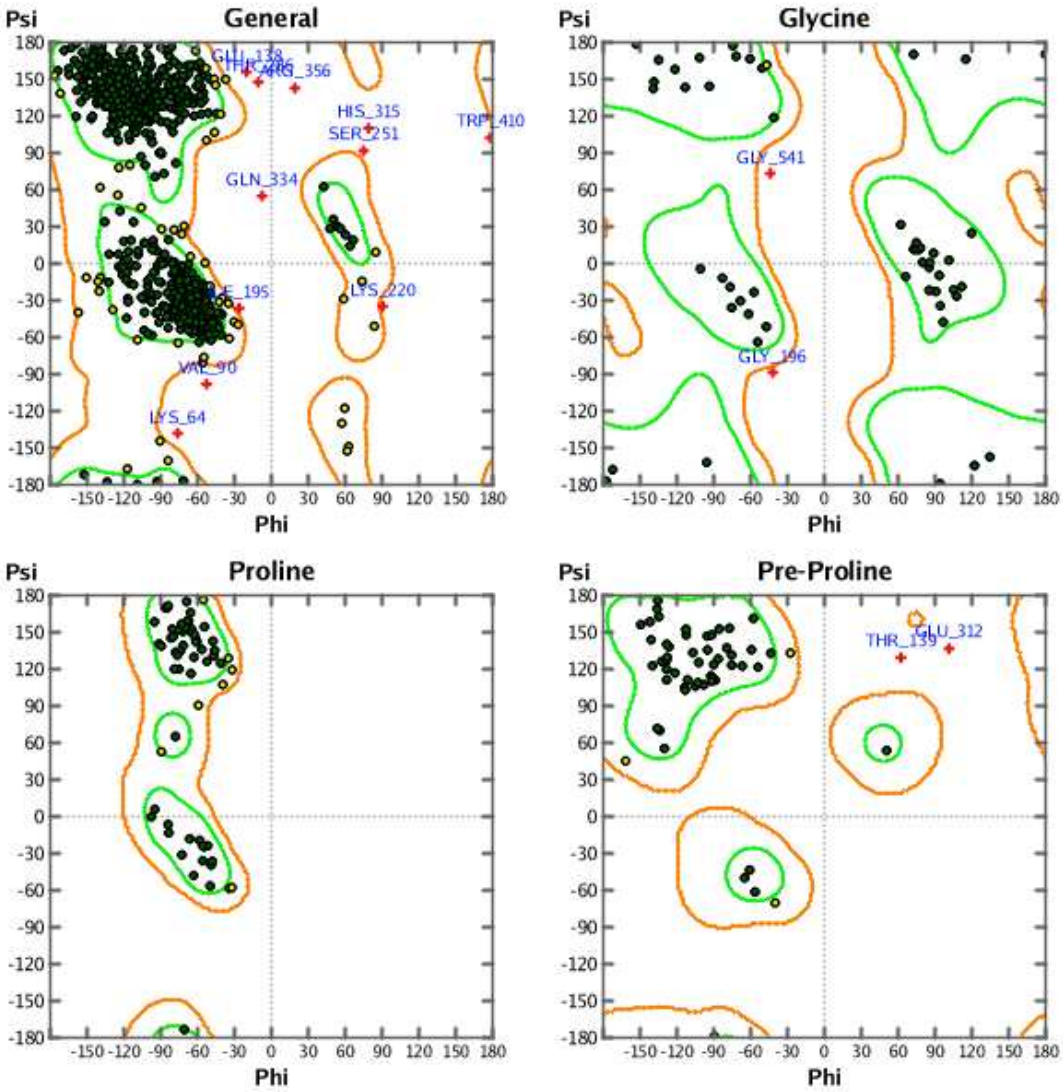

Figure2: Ramchandran plot of the PDB 3DRP

The structure of HIV-1 RT bound to different drugs has being solved by crystallography and different binding sites have been determined depending on the nature of the ligand counterparts as well as on the experimental conditions of the research. Docking procedures were performed on HIV-1 RT as receptor, downloading its structure from the Protein Data Bank (PDB). Different files of HIV-1 RT complexed with different ligands are available from that web site. We selected PDB file (PDB code: 3DRP) complexed with R8E.

The rationale of this selection is to choose the receptor with the ligand as similar as possible with 2-Amino-6-arylsulfonylbenzonitrile derivatives and located in the most active drug binding site. The structure of HIV-1 RT protein was obtained from Protein Data Bank [Research

Collaboratory for Structural Bioinformatics (RCSB) (http://www.rcsb.org/pdb)]. The structure was validated by plotting Ramchandran plot using "Protein Geometry" module in MOE, which shows that 91.93% of the residues are in the core region of the Ramachandran Map and Core: Score > 0.02 Allowed: 0.0005 <= Score <= 0.02 Outlier: Score < 0.0005 (Fig.2).

3.2 Docking Algorithms

Docking programs are of two classes, "direct" and "unbiased." Despite of the disadvantage of making assumptions about the potential energy landscape to save computational time direct docking softwares such as DOCK have the benefit of speed. Unbiased methods such as AutoDock, FTDOCK and MOE-Dock perform with few assumptions about the potential energy landscape. Thus at the expense of computation time, they find final docked solutions that the direct method might have missed. Here we report the use of MOE-Dock by Chemical Computing Group Inc. [15], which has the advantage flexible docking as well as integration with a graphical interface as well as with other modules, such as analysis, molecular mechanics, and molecular dynamics.

3.3 Docking Simulations

In MOE London dG scoring is used as default setting to calculate the exact confirmation and configuration of the ligand to find the best molecule with minimum binding energy [11] and it can be used to develop potential drug molecules against the disease. The London dG scoring function estimates the free energy ΔG of binding of the ligand from a given pose. The functional form is a sum of terms:

$$\Delta G = c + E_{flex} + \sum_{h-bonds} c_{HB} f_{HB} + \sum_{m-lig} c_M f_M + \sum_{atoms\ i} \Delta D_i$$

where C represents the average gain/loss of rotational and translational entropy; E_{flex} is the energy due to the loss of flexibility of the ligand (calculated from ligand topology only); f_{HB} measures geometric imperfections of hydrogen bonds and takes a value in [0,1]; C_{HB} is the energy of an ideal hydrogen bond; f_M measures geometric imperfections of metal ligations and takes a value in [0,1]; C_M is the energy of an ideal metal ligation; and D_i is the desolvation energy of atom i. The difference in desolvation energies is calculated according to the formula

$$\Delta D_i = c_i R_i^3 \left\{ \iiint_{u \notin A \cup B} |u|^{-6}\, du - \iiint_{u \notin B} |u|^{-6}\, du \right\}$$

Where A and B are the protein and/or ligand volumes with atom i belonging to volume B; R_i is the solvation radius of atom i (taken as the OPLS-AA van der Waals sigma parameter plus 0.5 Angstrom); and C_i is the desolvation coefficient of atom i. Atoms are categorized into ~12 atom types for the assignment of the C_i coefficients. MOE 2008.10 was run on a Windows XP based Pentium IV 2·66 GHz PC (with 1GB RAM).

3.4 Docking Run Parameters:

Since the main goal of this study was to perform docking to understand binding between ligand and receptor six molecules were chosen to get fruitful results. The list includes one highly active and one lowest active compound from each series .During docking most of the default settings were applied except that the number of *Retain* were 10 instead of 30 during docking in MOE. Protein structures were first repaired and then appropriately protonated in the presence of ligand using the Protonate3D [16] process in MOE. Proteins prepared in this manner were applied directly for docking. It is well documented in literature [17] that if a crystallographic structure of

the protein complexed with a relatively close analog of the ligand is available, "ligand-based docking" may be performed. In this procedure, one or more conformations of the candidate ligand are fitted to the crystallographic structure of the known ligand by optimizing the similarity in electrostatic and steric potentials. The experimental structure of the "template" ligand is then deleted, leaving the candidate ligand docked to the protein. In addition, the conformation of the fitted ligand may be simultaneously optimized during the fitting. The same strategy was used to get best docking results. The default procedure using Triangle Matcher placement method with London dG scoring was used for the docking runs.

3.5 Docking of the molecule set

With the assumption that the comparison of docking results obtained for most active and least active compounds from each series will give better structure based understanding, compound therefore compound S1, S2, SO1, SO2, OSO1, OSO2 were used for docking studies. Figure 3 contains best docking pose of each selected molecule and Table 2 contains docking scores and Table 3 contains calculated parameters obtained using MOE.

Table 2: Different results obtained after docking 2-Amino-6-arylsulfonylbenzonitrile derivatives in active site of HIV-1 RT along with other parameters calculated by MOE

Sr. No.	*1*	*2*	*3*	*4*	*5*	*6*
Code	S1	S2	SO1	SO2	OSO1	OSO2
pIC_{50}	-1.204	0.921	-1.279	0.301	-0.653	2.523
S	-11.3046	-12.3693	-12.6280	-12.2915	-11.9934	-12.4109
Econf	0.60	0.00	1.40	1.40	0.60	0.60
Eplace	-57.720	-60.426	-73.321	-70.176	-86.405	-68.234
Escore1	-11.3046	-12.3693	-12.6280	-12.2915	-11.9934	-12.4109

S: The final score, which is the score of the last stage that was not set to none. Econf: the energy of the conformer. Eplace: Score from the placement stage. Escore1: Score from the rescoring stage(s).

Table 3: Different parameters calculated by MOE before and after docking for the selected ligands

Code	*S1*	*S2*	*SO1*	*SO2*	*OSO1*	*OSO2*
E(x) Before	75.829	74.049	100.459	100.783	64.277	52.100
After	82.121	75.761	127.483	119.341	98.540	336.550
Estr Before	3.696	3.757	3.691	4.253	3.412	3.334
After	20.897	20.606	20.860	20.871	20.305	16.446
Eang Before	17.880	19.280	28.890	25.131	15.825	8.902
After	15.080	15.150	46.227	39.544	21.538	11.685
Estb Before	0.226	0.403	0.293	0.472	0.591	0.489
After	-0.368	-0.322	-2.558	-1.850	-0.862	1.823
Eoop Before	0.098	0.112	0.314	0.564	0.033	0.017
After	0.000	0.000	0.000	0.000	0.000	0.024
Etor Before	12.562	13.620	19.271	18.264	-2.325	-2.566
After	9.489	10.140	18.932	17.338	-0.147	-2.245
Evdw Before	43.966	45.446	49.796	50.229	40.790	36.112
After	39.420	38.593	44.084	44.816	50.588	308.818
Eele Before	-2.600	-8.568	-1.797	1.871	5.951	5.813
After	-2.398	-8.407	-0.061	-1.377	7.117	0.000
Eres Before	0.000	0.000	0.000	0.000	0.000	0.000
After	0.000	0.000	0.000	0.000	0.000	0.000
TPSA	49.810	49.810	95.320	86.090	93.180	83.950
logP	3.945	4.598	2.316	2.924	1.982	3.044

Where E(x): potential energy of a molecular system Estr: bond stretch energy Eang: bond angle bend energy Estb: stretch-bend energy Eoop: out-of-plane energy Etor: Dihedral angle or torsion energy Evdw: van der Waals energy Eele: electrostatics energy Eres: restraint energy.

The parameters like E(x), Estr, logP and other were calculated for selected ligand before and after docking. For this the ligand was protonated and tethered using "LigX" module in MOE and various parameters were calculated before docking, after docking the parameters were calculated directly without doing protonation and tether. All calculated parameters are listed in table 3. Analysis of the table 3 indicates that the calculated logP for all the selected compound is below five which means these are good choice as drug candidate. Moreover, the values of E(x) which is function of the atomic coordinates and calculated by the formula:

$$E(x) = E_{str} + E_{ang} + E_{stb} + E_{oop} + E_{tor} + E_{vdw} + E_{ele} + E_{sol} + E_{res}$$

Where each of the energy terms is itself a sum involving different types of atomic interactions, indicates that the lowest energy conformation is not the *best pose* conformation. For most active compound OSO2 the value of Evdw has very large difference before and after docking indicating substantial van der Waal interactions between ligand and protein and this may be the reason behind its high activity. Since other ligands are also showing van der Waal interactions with various amino acids in binding pocket it seem that van der Waal interactions are necessary for their binding. Hydrogen bonding is represented by dotted line

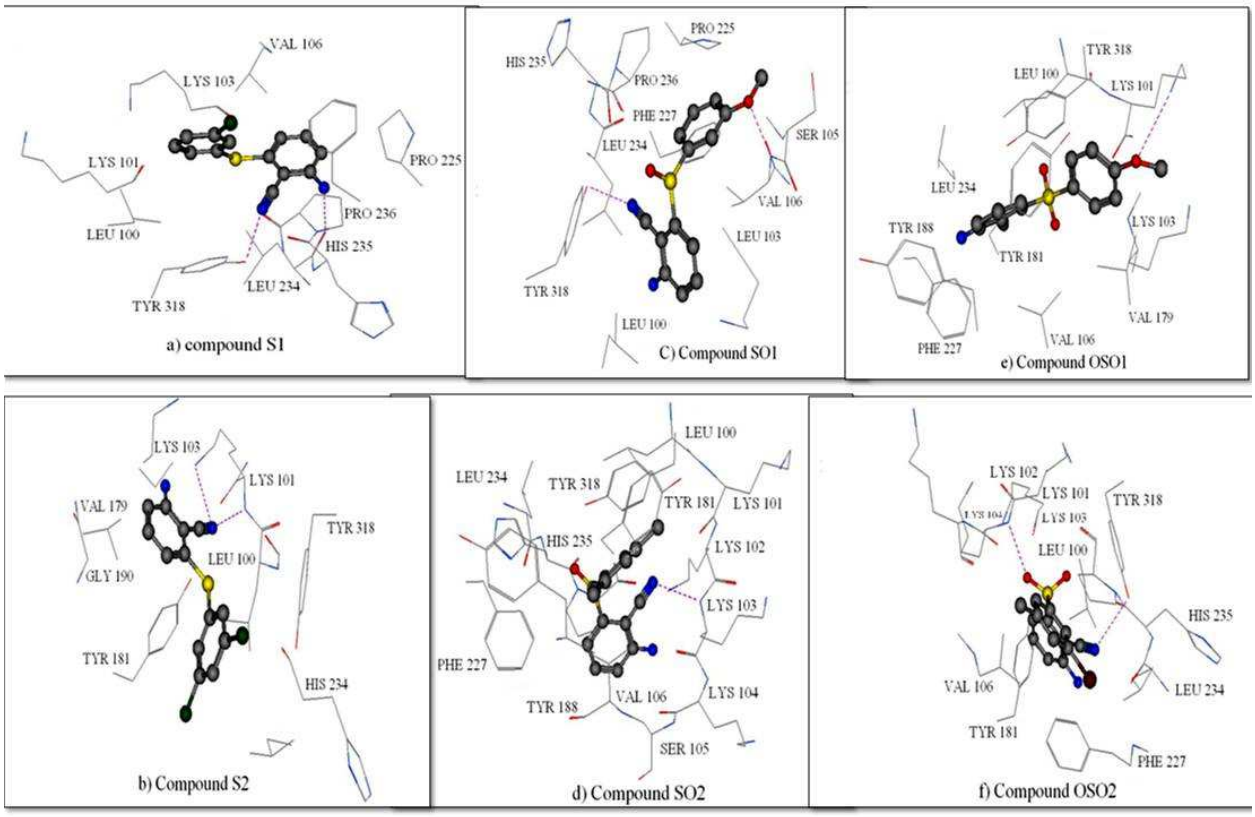

Figure 3: Docking poses of different 2-Amino-6-arylsulfonylbenzonitrile derivatives.

RESULTS AND DISCUSSIONS

The NNRTIs rapidly lead to the appearance of drug-resistant HIV-1 mutants, both *in vitro* as well as *in vivo*. The mutations that cause resistance to the NNRTIs appear to be located at positions 98, 100, 101, 103, 106, 108, 179, 181, 188, 190, 230, and 236 of the p66 subunit, and position 138 of the p51 subunit, of the HIV-1 reverse transcriptase. The most notorious is the 181 Tyr → Cys mutations that lead to resistance to almost all NNRTIs. Under the continued pressure of the NNRTIs the 181 Tyr → Cys mutants can further mutate to the 181 Cys → Ile mutant,

which is even more resistant to the drugs. Mutations may also appear/disappear in a controlled fashion so as to import a higher level of resistance, as has been noted with the 106 Val → Ala mutation that was replaced by the 190 Gly → Glu mutation under increased pressure of the drug (i.e., quinoxaline S-2720).

The fact that the different classes of NNRTIs give rise to different resistance mutations may be interpreted to mean that they interact with different affinities or different amino acid residues within the NNRTI-binding site [17]. This suggests that the different NNRTIs should not necessarily lead to cross-resistance.

From the docking it is clear that the side chain and backbone of residue surrounding the active site adjust to each bound drug with each drug by different amount this suggests that the conformation of receptor changes on introduction of drug at active site. This means this protein is able to interact and accommodate inhibitors of different chemical structures. The results demonstrate that 2-Amino-6-arylsulfonylbenzonitrile derivatives can be docked and aligned into the NNRTI allosteric binding site extremely well.

The docking studies reveal that like other NNRTIs, 2-Amino-6-arylsulfonylbenzonitrile derivatives also bind with protein in a “Butterfly-like” mode and introduce short range conformational changes in protein. All the ligands exhibited van der Waals interactions with various amino acids in p66 subunit.

The most active compound OSO2 binds to protein not only due to hydrogen bonding but due to hydrophobic and electrostatic interactions also. It binds with Tyr 318 and Lys 103 through hydrogen bonding whereas the compound OSO1 which shows hydrogen bonding with Lys 101 through oxygen of $–OCH_3$ group and no hydrogen bonding due to oxygen of $-SO_2$ group and –CN group.

Table 4: Antiviral Activity of Representative 2-Amino-6-arylsulfonylbenzonitriles NNRTIs against HIV-1 Wild-Type and MutantViruses [14]

Sr. No.	*virus/compds*	*OSO18*	*OSO2*
1	wild-type	0.037	0.009
2	K103N	8.3	0.97
3	V106A	0.0062	0.0015
4	Y181C	50	10
5	V106A/Y181C	1.8	0.077
6	E138K	0.085	0.015
7	G190A	0.084	0.031
8	V108I/Y181C	58	18
9	V108I	0.047	0.011
10	Y188C	0.14	1.7
11	K103N/L100I	5.5	16
12	P236L	0.0025	0.011
13	K103N/Y181C	>50	>50
14	K103N/V108I	4	15
15	K103N/P225H	3.8	13

Analysis of table 4 clears that if mutation is V108I/Y181C than the activity of OSO2 decreases significantly, same is true for OSO18. This fact support our docking results that active compound bind to the protein through Y181 using π–π interactions. To add further the mutation K103N/V108I or K103N/P225H causes a noteworthy decrease in activity of OSO2 indicating that ligand binds to protein through K103 or V108 or P225. This not only suggests that

interaction with K103 is very important for binding but again confirms results of our docking studies also that compound OSO2 binds with Tyr 318 and Lys 103 through hydrogen bonding. Whereas earlier docking studies by Chen [14] indicated that the ligands bind to protein through carbonyl oxygen of amino acid K101.

Compound SO2 shows hydrogen bonding through –CN with Lys 103 but compound SO1 shows two hydrogen bonds one with Tyr 318 through –CN and other with the Val 106 through $–OCH_3$ group. Compound S2 shows hydrogen bonding with Tyr 318 and Lys 101 through –CN group but compound S1 shows two hydrogen bondings one through –CN with Tyr 318 and other with Leu 234 through $–NH_2$ group. But due to additional –Cl the hydrophobic interactions are very high. The presence of hydrophobic group like $–CH_3$ at position 4 and 5 increases activity considerably hence retention of $–CH_3$ at position 4 &/or 5 is highly favorable. The presence of –Br at position 3 has positive impact but negative impact at position 2, therefore in future drug development it should be retained at position 3.

The amino acids in the binding pocket of RT enzyme are mainly lipophilic with aromatic residues [18]. Therefore, not only hydrogen bonding but hydrophobic interactions also play vital role in deciding anti-HIV activity [19]. Hydrogen bonding plays activity enhancing role if it is between –CN and Tyr 318. Extensive hydrophobic interactions are instrumental in stabilizing the 2-Amino-6- arylsulfonylbenzonitrile derivatives. As expected, the major role is played by the aromatic moiety present in the structure. π–π interactions are observed between the aromatic moieties of the amino acid residues that converge at the inner side of the binding cavity and the aromatic moieties of the ligand. The electrostatic interaction is stabilized by these stacking type interactions. As stated earlier 181 Tyr → Cys mutation is responsible for resistance and none of the 2-Amino-6- arylsulfonylbenzonitrile derivatives binds to protein through this amino acid therefore 2-Amino-6- arylsulfonylbenzonitrile derivatives are good candidates for future drug designing for resistant HIV-1 viruses. To conclude, the docking studies provide understanding on the binding interaction of the 2-Amino-6- arylsulfonylbenzonitrile derivatives and could be useful for developing new strategies for novel inhibitor design to speed up the drug discovery process. Finally, the docking studies performed here suffer from the limitations associated with the approximations inherent to simplified empirical models and qualms associated with protein structure.

Acknowledgment
We are thankful to Mr. MeghShyam Patil, IICT, Hyderabad, India, Mr. Mangesh Tihile, National Chemical laboratory, Pune, India and Naseer Baig, Indian Institute of Science, Banglore, India for providing data, substantial computational work and helpful discussions.

REFERENCES

[1] N. S Sapre, S. Gupta, N. Sapre, *J. Chem. Sci*., **2008**, 120, 395–404.
[2] Rahul D. Jawarkar, Vijay H. Masand, Komalsingh N. Patil, Devidas T. Mahajan, Moulay Hfid Youssoufi, Taibi Ben Hadda, Santosh L. Kumbhare, *Der Pharma Chemica*, **2010**, 2(6): 302-310
[3] Rahul D. Jawarkar, Devidas T. Mahajan, Vijay H. Masand, Taibi Ben Hadda, G. H. Kurhade, *Der Pharmacia Lettre*, **2010**, 2(6):350-357
[4] Anil M. Manikrao, Pravin N. Khatale, Rahul D. Jawarkar, J. V. Vyas, D. T. Mahajan, Vijay H. Masand, Taibi ben hadda, *J. Comput. Method. Mol. Design*, **2011**, 1 (2):9-13
[5] G. M. Nazeruddin, S. B. Suryawanshi, Hassan A. Osman, Vijay H. Masand, Komalsingh N. Patil, *J. Chem. Pharm. Res*., **2010**, 2(3):544-550

[6] Vijay H. Masand, Komalsingh N. Patil, Devidas T. Mahajan, Rahul D. Jawarkar, Ghulam M. Nazerruddin, *Der Pharma Chemica*, **2010**, 2(4): 298-308
[7] V. H. Masand, K. N. Patil, G. M. Nazerruddin, R. D. Jawarkar, S. O Bajaj., *Org. Chem*.: An Ind. J., **2010**, 6(1), 30-38
[8] C. Sahlberg, X. X. Zhou, *Anti-Infect. Agents Med. Chem*., **2008**, 7, 101-117.
[9] N. S. Cremer, N. A. Temiz, I. Bahar, *Curr. HIV Res*., **2004,** 2, 323-332.
[10] S. Ravichandran , R. Veerasamy, S. N. Krishnan, R. K. Agrawal, *Dig. J. Nanomat. Biostruct*., **2008**, 3, 171 – 187.
[11] E. DeClercq, A. Karlsson, J. Balzarini, In; E. A. Rekka P. N. Kourounakis, Chemistry And Molecular Aspects Of Drug Design And Action , CRC Press Taylor & Francis Group, LLC, **2008**, pp177-198.
[12] V. Mohan, A. C. Gibbs, M. D. Cummings, E. P. Jaeger, R. L. DesJarlais, *Curr. Pharma. Design*, **2005**, 11, 323-333.
[13] A. Ivetac, J. A. McCammon, *J. Mol. Biol*., **2009**, 388, 644–658.
[14] J. H. Chan, J. S. Hong,R. N. Hunter, G. F. Orr, J. R. Cowan, D. B. Sherman, S. M. Sparks, B. E. Reitter, C. W. Andrews, R. J. Hazen, M. St Clair, L. R. Boone, R. G. Ferris, K. L. Creech, G. B. Roberts, S. A. Short, K. Weaver, R. J. Ott, J. Ren, A. Hopkins, D. I. Stuart, D. K. Stammers, *J. Med. Chem*., **2001**, 44, 1866-1882.
[15] MOE Molecular Operating Environment, Version 2008; Chemical Computing Group Inc.: Montreal, Canada, **2008.**
[16] H. Singh, S. S. Marla, M. Agarwal, IAENG *Int. J. Comp. Sci*., **2007**, 33(1), 1-7.
[17] N. C. Cohen, Guidebook on Molecular modeling in Drug Design, Academic Press, **1996**, 253-257.
[18] B. Hemmateenejad, S.M.H. Tabaei, F. Namvaran, *J. Iran. Chem. Soc*., **2007**, 4(4), 481-489.
[19] N. S. Cremer, N. A. Temiz, I. Bahar, *Curr. HIV Res*., **2004,** 2, 323-332.