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IN SILICO MOLECULAR DOCKING STUDIES ON THE NOVEL SUBSTITUTED BENZENE SULFONAMIDO-N-HYDROXYBENZAMIDE DERIVATIVES AGAINST HIV REVERSE TRANSCRIPTASE

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ABSTRACT

Human Immunodeficiency Virus (HIV) remains one of the most serious global health threats. HIV causes a progressive failure of immune system which can lead to AIDS and other chemotherapy of AIDS patients. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), there were approximately 38.4 million people across the globe with HIV in 2021. HIV type 1 reverse transcriptase is one of the most attractive targets in the chemotherapy of AIDS patients. Sulfonamides constitute an important class of drugs possessing antibacterial, diuretic, hypoglycemic, anticancer, anti-viral activity etc. Molecular docking has become an integral part of CADD and is used to position the computer-generated 3D structure of small ligands into a receptor structure. In this study we have designed and docked aryl sufonamide derivatives against Non-nucleoside reverse transcriptase enzyme to evaluate their anti HIV activity. Molecular modeling was carried out using Sybyl-X, version 2.1, running on Intel Core™ i3-2130 CPU at 3.40GHz processor using Windows 7 professional workstation. The Surflex-Dock algorithm of Sybyl-X 2.1 was used. Sulfonamide derivatives with the electron donating group on the benzene ring were found to have good docking score value compared to the derivatives with the electron withdrawing group on the benzene ring. Benzene ring substituted with two electron

withdrawing substituent groups were also found to have less docking score value. Our study indicates that aryl sulfonamide derivative have potential anti HIV activity against reverse transcriptase enzyme. Some of the derivative was found to have good docking score value and binding affinity compared to standard drug. Derivatives with the good docking score value will be synthesized in future.

KEYWORDS: Aryl Sulfonamide derivatives, NNRTIs, HIV, molecular docking, Glide score.

INTRODUCTION

Human Immunodeficiency Virus (HIV) remains one of the most serious global health threats. HIV causes a progressive failure of immune system which can lead to Acquired Immunodeficiency Syndrome (AIDS), which can also lead to subsequent increased vulnerability to infections and other immunological disorders and increased risk for different types of cancer. In India, the first case of HIV was reported in 1986 since then the epidemic has grown rapidly.[1] According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), there were approximately 38.4 million people across the globe with HIV in 2021. Of these, 36.7 million were adults and 1.7 million were children (<15 years old). In addition, 54% were women and girls.[2]

Human immunodeficiency virus type 1 reverse transcriptase (HIV-1 RT) is one of the most attractive targets in the chemotherapy of AIDS patients and hence HIV-1 RT inhibitors play a vital role in HIV/AIDS effective therapy, the highly active antiretroviral therapy (HAART).[3]

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) nowadays represent very potent and most promising anti-AIDS agents that specifically target the HIV-1 reverse transcriptase (RT). However, the effectiveness of NNRTI drugs can be hampered by rapid emergence of drug-resistant viruses and severe side effects upon long-term use. Therefore, there is an urgent need to develop novel, highly potent NNRTIs with broad spectrum antiviral activity and improved pharmacokinetic properties, and more efficient strategies that facilitate and shorten the drug discovery process which would be extremely beneficial. Fortunately, the structural diversity of NNRTIs provided a wide space for novel lead discovery, and the pharmacophore similarity of NNRTIs gave valuable hints for lead discovery and optimization.[4]

Sulfonamides constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial, anti-carbonic anhydrase, diuretic, hypoglycemic, anti-thyroid and anticancer activity among others. A large number of structurally novel sulfonamide derivatives have ultimately been reported to show substantial antiviral activity in vitro and in vivo.[5] Sulfonamide derivatives have shown promise as NNRTIs for the treatment of HIV infection. While more research is needed to fully understand their mechanism of action and potential side effects, these compounds have already made a significant impact in the fight against HIV/AIDS.

Docking has become an integral part of Computer-Aided Drug Design and Discovery (CADDD). Molecular Docking is used to position the computer-generated 3D structure of small ligands into a receptor structure in a variety of orientations, conformations and positions. This method is useful in drug discovery and medicinal chemistry providing insights into molecular recognition.[6] Docking studies have been useful in understanding the molecular interactions between sulfonamide derivatives and RT, and have contributed to the discovery and optimization of new NNRTIs for the treatment of HIV infection. In view of these observations it was thought of interest to undertake the design and docking study of compounds having aryl sulphonamide moiety and evaluate their anti HIV activity by non nucleoside reverse transcriptase enzyme inhibitor.

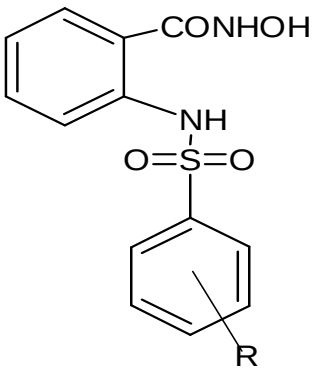
MATERIALS AND METHODS

Molecular modeling was carried out using Sybyl-X, version 2.1, running on Intel® Core™ i3-2130 CPU at 3.40GHz processor using Windows 7 professional workstation.[7] The Surflex-Dock algorithm of Sybyl-X 2.1 was used to dock designed compounds. The Crystal structure of HIV reverse transcriptase Y181C mutant in complex with inhibitor R8e was downloaded from the Protein Data Bank (PDB entry code 3DR). PDB extracted from the Brookhaven Protein Database (http://www.rcsb.org/pdb) and used for initial docking studies. The co-crystallized ligand was removed from the structure, water molecules were removed, essential H atoms were added and side chains were fixed during protein preparation. The structure was then subjected to an energy refinement procedure. Gasteigere-Huckel charges were calculated for the ligand, while Amber7FF02 was used for the protein.[8] The model was then subjected to energy minimization following the gradient termination of the Powell method for 3000 iterations using the Tripos force field with a non-bonding cutoff set at 9.0 and the dielectric constant set at 4.0. Deliveridine was used as the standard drug for comparison. The binding of

the standard drug and substituted aryl sulphonamide derivatives were estimated using a variety of scoring functions that have been compiled into the single consensus score (C Score).

RESULTS AND DISCUSSION

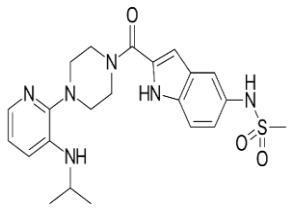
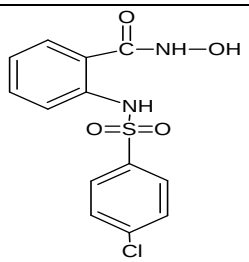
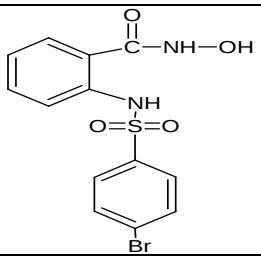
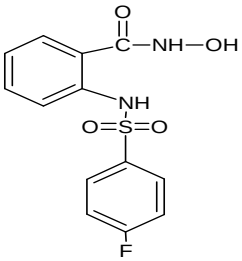
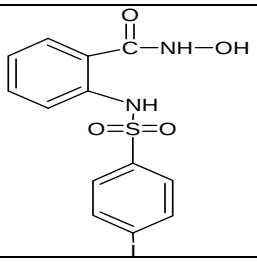
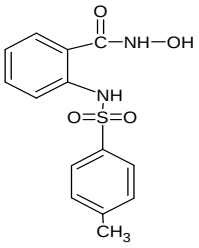
To investigate the detailed intermolecular interactions between the ligand and the target protein, a program Surflex-Dock was used. Three-dimensional structure information on the target protein was taken from the PDB entry 3DRR. Processing of the protein included the deletion of the ligand and the solvent molecules as well as the addition of hydrogen atoms. Standard and all the 36 proposed inhibitors were docked into the active site of the enzyme. The predicted binding energies of the compounds are listed in Table 2. Figures 2A & 2B shows the docking mode of compound 10 and figures 3A & 3B represents the binding mode of compound 6 at the active site of the enzyme. As depicted in the Figures 2A and 2B in the compound 10, the carbonyl group of -CONHOH chain at *meta*-position of aromatic ring shows hydrogen binding with hydrogen of LYS103 and another hydrogen bonding was with amino acid residue PRO236 and hydrogen of -CONHOH. As depicted in the Figures 3A and 3B of compound 6, the carbonyl group of -CONHOH chain at *meta*-positon of aromatic ring shows two hydrogen binding interactions with hydrogen of LYS102 and LYS103 and hydroxyl group of -CONHOH shows two hydrogen bonding interaction with LYS102 and LYS103.

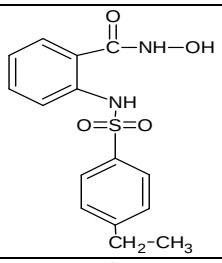
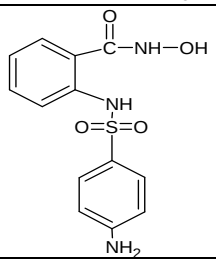
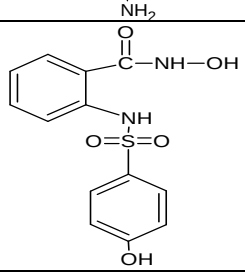
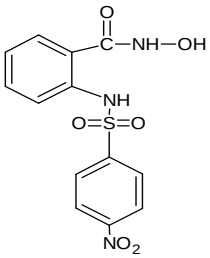
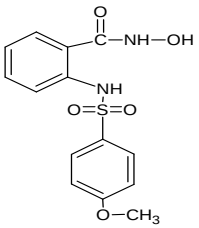
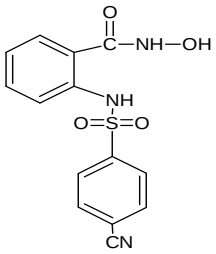
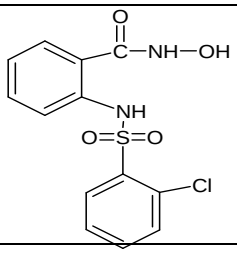


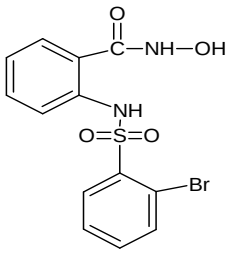
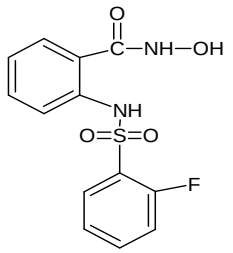
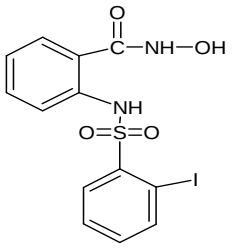
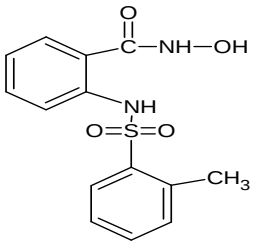
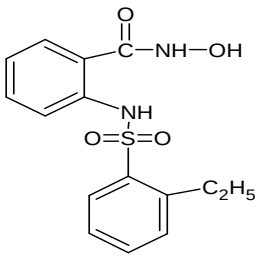
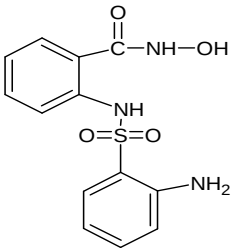
R- various electron donating or electron withdrawing substituents

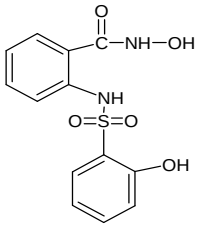
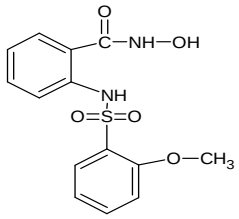
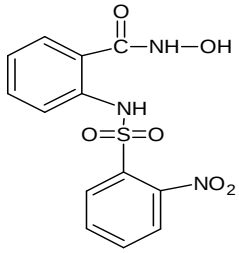
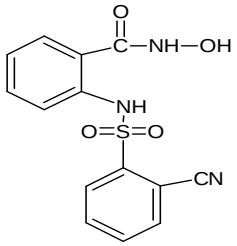
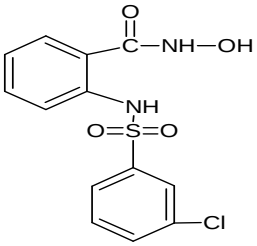
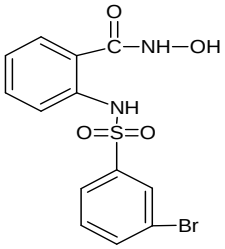
Fig 1: Structure of the pharmacophore.

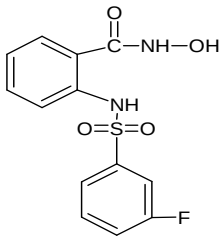
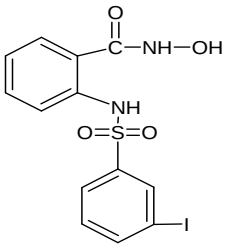
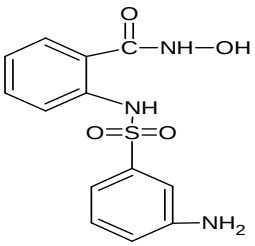
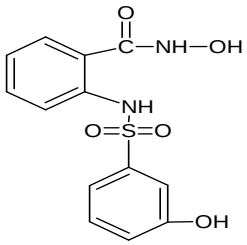
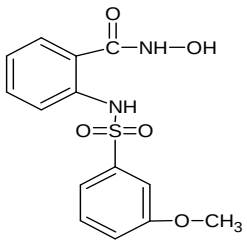
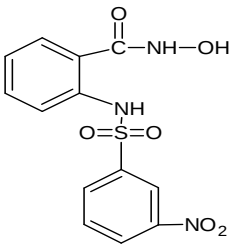
Table 1: Structures of the proposed aryl sulphonamide derivatives

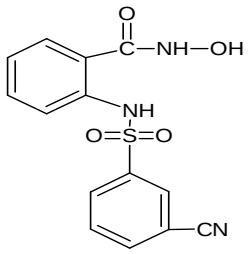
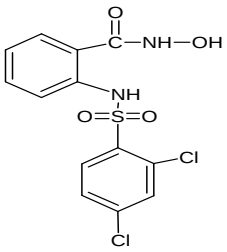
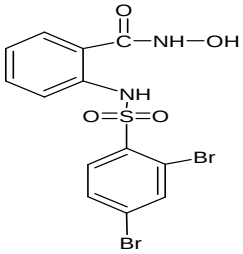
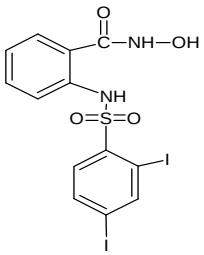
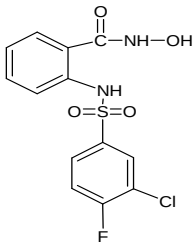
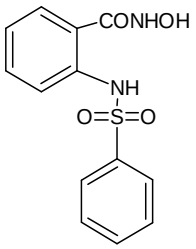
S.No	Compounds	IUPAC Name	Structure	Nature of the varying substitutent group
1.	**Standard (Deliviridine)**	*N*-[2-[4-[3-(propan-2-ylamino)pyridin-2-yl]piperazine-1-carbonyl]-1*H*-indol-5-yl]methanesulfonamide		Heterocyclic rings.
2.	CPD 1	2-(4-chlorobenzene sulfonamido)-N-hydroxybenzamide		(*p*-EWG)
3.	CPD 2	2-(4-bromobenzene sulfonamido)-N-hydroxybenzamide		(*p*-EWG)
4.	CPD 3	2-(4-fluorobenzene sulfonamido)-N-hydroxybenzamide		(*p*-EWG)
5.	CPD 4	2-(4-iodobenzene sulfonamido)-N-hydroxybenzamide		(*p*-EWG)
6.	CPD 5	2-(4-methylbenzene sulfonamido)-N-hydroxybenzamide		(*p*-EDG)

7.	CPD **6**	2-(4-ethylbenzene sulfonamido)-N-hydroxybenzamide		(*p*-EDG)
8.	CPD 7	2-(4-aminobenzene sulfonamido)-N-hydroxybenzamide		(*p*-EDG)
9.	CPD 8	2-(4-hydroxybenzene sulfonamido)-N-hydroxybenzamide		(*p*-EDG)
10.	CPD 9	2-(4-nitrobenzenesulfonamido)-N-hydroxybenzamide		(*p*-EWG)
11.	CPD **10**	2-(4-methoxybenzene sulfonamido)-N-hydroxybenzamide		(*p*-EDG)
12.	CPD 11	2-(4-cyanobenzene sulfonamido)-N-hydroxybenzamide		(*p*-EWG)
13.	CPD 12	2-(2-chlorobenzene sulfonamido)-N-hydroxybenzamide		(*o*-EWG)

14.	CPD 13	2-(2-bromobenzene sulfonamido)-N-hydroxybenzamide		(*o*-EWG)
15.	CPD 14	2-(2-fluorobenzene sulfonamido)-N-hydroxybenzamide		(*o*-EWG)
16.	CPD 15	2-(2-iodobenzene sulfonamido)-N-hydroxybenzamide		(*o*-EWG)
17.	CPD 16	2-(2-methylbenzene sulfonamido)-N-hydroxybenzamide		(*o*-EDG)
18.	CPD 17	2-(2-ethylbenzene sulfonamido)-N-hydroxybenzamide		(*o*-EDG)
19.	CPD 18	2-(2-aminobenzene sulfonamido)-N-hydroxybenzamide		(*o*-EDG)

20.	CPD 19	2-(2-hydroxybenzene sulfonamido)-N-hydroxybenzamide		(*o*-EDG)
21.	CPD 20	2-(2-methoxybenzene sulfonamido)-N-hydroxybenzamide		(*o*-EDG)
22.	CPD 21	2-(2-nitrobenzene sulfonamido)-N-hydroxybenzamide		(*o*-EWG)
23.	CPD 22	2-(2-cyanobenzene sulfonamido)-N-hydroxybenzamide		(*o*-EWG)
24.	CPD 23	2-(3-chlorobenzene sulfonamido)-N-hydroxybenzamide		(*m*-EWG)
25.	CPD 24	2-(3-bromobenzene sulfonamido)-N-hydroxybenzamide		(*m*-EWG)

26.	CPD 25	2-(3-fluorobenzene sulfonamido)-N-hydroxybenzamide		(*m*-EWG)
27.	CPD 26	2-(3-iodobenzene sulfonamido)-N-hydroxybenzamide		(*m*-EWG)
28.	CPD 27	2-(3-aminobenzene sulfonamido)-N-hydroxybenzamide		(*m*-EDG)
29.	CPD 28	2-(3-hydroxybenzene sulfonamido)-N-hydroxybenzamide		(*m*-EDG)
30.	CPD 29	2-(3-methoxybenzene sulfonamido)-N-hydroxybenzamide		(*m*-EDG)
31.	CPD 30	2-(3-nitrobenzene sulfonamido)-N-hydroxybenzamide		(*m*-EWG)

32.	CPD 31	2-(3-cyanobenzene sulfonamido)-N-hydroxybenzamide		(*m*-EWG)
33.	CPD 32	2-(2,4-dichlorobenzene sulfonamido)-N-hydroxybenzamide		(*o,p*-EWG)
34.	CPD 33	2-(2,4-dibromobenzene sulfonamido)-N-hydroxybenzamide		(*o,p*-EWG)
35.	CPD 34	2-(2,4-diiodobenzene sulfonamido)-N-hydroxybenzamide		(*o,p*-EWG)
36.	CPD 35	2-(3-chloro-4-fluorobenzene sulfonamido)-N-hydroxybenzamide		(*m,p*-EWG)
37.	CPD 36	Benzenesulfonamido-N-hydroxybenzamide		unsubstituted

o-ortho, *m*-meta, *p*-para, EWG-Electron Withdrawing Group, EDG-Electron Donating Group

Table 2: Surflex Docking score value (kcal/mol) of the aryl sulphonamide derivatives.

Compounds	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	Chem Score[g]
Stanadard (Deliviridine)	**5.00**	**-1.4639**	**2.1624**	**-759.9765**	**-23.2097**	**-194.1282**	**-40.661**
CPD 1	4.76	-1.34	3.83	-207.23	-25.18	-154.42	-33.46
CPD 2	4.67	-1.34	3.15	-198.41	-19.96	-157.24	-34.18
CPD 3	4.64	-1.45	3.24	-239.30	-18.89	-158.77	-33.86
CPD 4	4.56	-1.30	3.13	-197.52	-23.16	-153.21	-34.48
CPD 5	4.93	-1.19	2.32	-196.23	-5.50	-173.28	-36.05
CPD **6**	**5.42**	**-2.13**	**2.20**	**-225.30**	**2.41**	**-213.06**	**-35.65**
CPD 7	5.31	-1.29	4.14	-254.40	-28.84	-151.96	-37.12
CPD 8	4.78	-1.38	4.17	-267.79	-23.02	-159.19	-35.57
CPD 9	4.53	-1.46	4.31	-451.09	-26.88	-143.97	-31.77
CPD **10**	**5.43**	**-0.58**	**1.08**	**-363.20**	**-23.89**	**-159.16**	**-31.35**
CPD 11	4.22	-0.60	1.54	-233.44	-25.59	-139.73	-31.98
CPD 12	4.24	-1.21	3.04	-151.33	-22.81	-165.75	-38.61
CPD 13	4.37	-1.40	1.15	-200.48	-20.27	-165.20	-31.54
CPD 14	4.45	-1.48	2.57	-251.94	-15.52	-157.70	-36.00
CPD 15	4.41	-1.49	2.57	-265.12	-20.78	-177.38	-37.04
CPD 16	5.04	-0.83	1.67	-190.01	-20.81	-154.59	-34.65
CPD 17	5.31	-1.00	1.61	-188.71	-20.85	-173.64	-33.68
CPD 18	5.08	-1.74	3.99	-271.51	-28.08	-163.82	-36.05
CPD 19	5.05	-1.70	3.95	-270.40	-27.08	-165.95	-37.05
CPD 20	4.97	-2.21	2.56	-326.18	-1.79	-179.99	-38.63
CPD 21	4.20	-2.23	3.58	-434.09	1.76	-174.15	-35.23
CPD 22	4.47	-0.92	2.41	-283.19	-25.48	-170.07	-33.62
CPD 23	4.64	-1.26	2.48	-172.91	-5.48	-169.81	-31.67
CPD 24	4.76	-1.28	2.65	-169.22	-8.97	-174.08	-32.87
CPD 25	4.78	-1.19	3.17	-208.38	-11.39	-147.43	-33.05
CPD 26	4.52	-1.10	3.22	-202.16	-31.57	-158.86	-37.32
CPD 27	5.15	-1.56	4.05	-275.15	-32.69	-152.69	-39.05
CPD 28	5.20	-1.16	4.32	-283.81	-34.29	-154.53	-35.83
CPD 29	5.04	-2.15	0.74	-391.36	-2.67	-162.76	-34.71
CPD 30	4.68	-1.20	2.90	-429.02	-31.92	-161.69	-33.60
CPD 31	4.75	-1.13	2.37	-276.17	-17.09	-164.78	-32.94
CPD 32	3.93	-0.83	1.93	-165.47	-24.11	-140.19	-38.62
CPD 33	4.01	-1.32	2.14	-151.67	-15.58	-169.14	-37.89
CPD 34	4.40	-1.31	2.22	-210.58	-3.24	-199.25	-38.10
CPD 35	4.59	-1.13	3.06	-263.63	-23.36	-156.90	-34.71
CPD 36	4.62	-0.96	2.90	-213.42	-23.75	-149.75	-34.55

a - C Score (Consensus Score) integrates several popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of the total score.

b - Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to zero are favorable. Negative numbers indicate penetration.

c - Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds.

d - D-score for charge and van der Waals interactions between the protein and the ligand.[9]

e - PMF-score indicating the Helmholtz free energies of interactions for protein-ligand atom pairs.[10]

f - G-score showing hydrogen bonding, complex (ligand-protein), and internal (ligand-ligand) energies.[11]

g - Chem-score points for hydrogen bonding, lipophilic contact, and rotational entropy, along with an intercept term.[12]

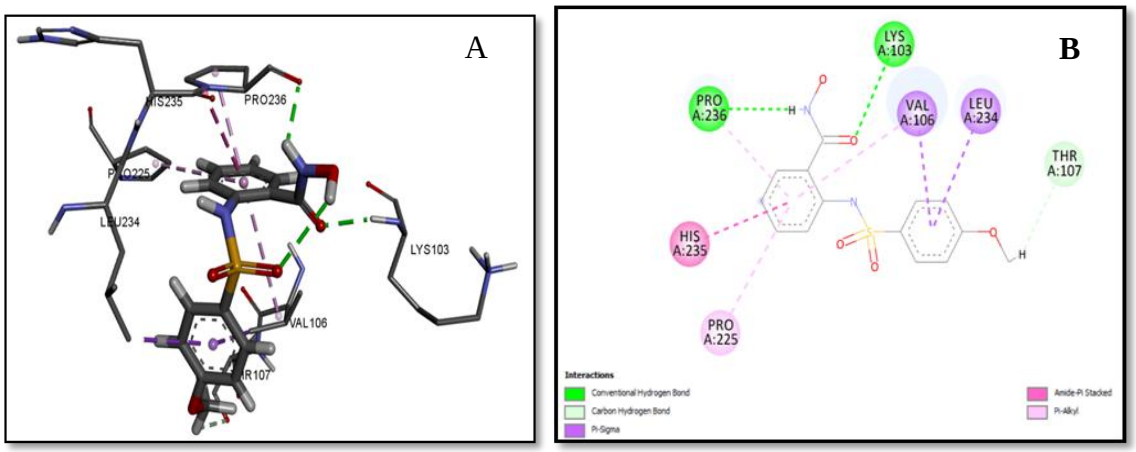


Fig 2A & 2B: Binding interaction of Compound 10 at the active site of the enzyme PDB ID 3DRR.

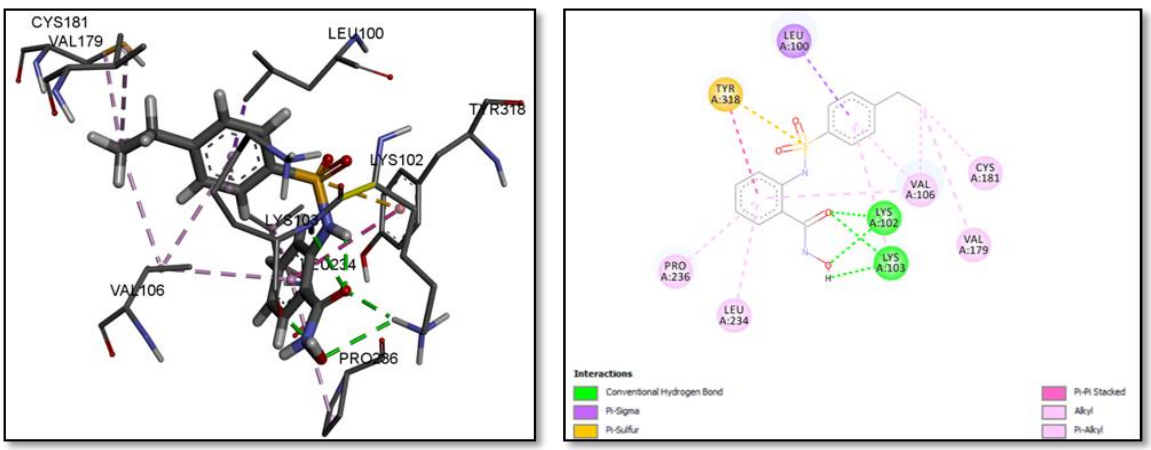


Fig 3A & 3B: Binding interaction of Compound 6 at the active site of the enzyme PDB ID 3DRR.

CONCLUSION

HIV-1 RT is essential for viral replication as it is responsible for conversion of its genomic single stranded RNA(ssRNA) into double stranded DNA(dsDNA) the provirus, which initiates the viral replication process. HIV-1 RT has a flexible structure and contains two known sites where drugs can bind: first is the active binding site, characterized by its catalytic triad, Asp110, Asp185, Asp186, where deoxynucleoside triphosphates bind in the normal procedure, and the second is an allosteric site or non-nucleoside inhibitor binding pocket (NNIBP), characterized by hydrophobic amino acid residues, and located about 10 Å away from the catalytic or active site.[13,14]

Our study indicates that aryl sulfonamide derivatives have potential anti HIV activity against reverse transcriptase enzyme. Aryl Sulfonamide derivatives with the electron donating groups (methoxy, methyl, ethyl, amino, hydroxyl groups etc) on the benzene ring were found to have good docking score value compared to the derivatives with the electron withdrawing group (halogens, nitro, cyano groups etc) on the benzene ring. Benzene ring substituted with two electron withdrawing substituent groups were also found to have less docking score value. Some of the derivatives were found to have good docking score value and binding affinity compared to standard drug. Derivatives with the good docking score value will be synthesized in future.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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