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ORIGINAL ARTICLE **OPEN ACCESS**

Molecular Docking Studies for Identification of Anti-HIV Ligand Against for Mutant Hiv-1 Reverse Transcriptase Protein

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ABSTRACT
The human immunodeficiency virus (HIV) is a lentivirus (a type of retrovirus) that causes acquired immunodeficiency syndrome (AIDS), a condition in which a person's immune system begins to fail, resulting in life-threatening infections. HIV is divided into two forms, the first of which is highly transmissible. As a result, the molecular docking method was employed to develop a medication to treat HIV. Docking was performed using the PDB crystal structure of mutant HIV-1 reverse transcriptase protein and the Pubchem database's small molecule (Multiflorenol). Small compounds have the lowest docking score of -8.1. TRP88, ALA158, VAL8, and PRO9 are the HIV RT's interaction residues. The MD simulation tests also showed that the newly developed compounds might stably bind to the HIV-1 RT. These hit compounds were meant to be unique potential anti-HIV-1 inhibitors, and the findings could help with the design and development of new HIV-1 RTs.
Keywords: AIDS, HIV-1 Reverse transcriptase, Multiflorenol, Molecular docking, Anti HIV-1

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INTRODUCTION

The human immunodeficiency virus (HIV) causes acquired immune deficiency syndrome (AIDS), which is one of the most widely disseminated infectious diseases on the planet. Currently, there is no viable medicine or vaccine that can completely treat AIDS. Currently, two forms of HIV (HIV-1 and HIV-2) have been recognized. HIV-1 is widely distributed over the world, whereas HIV-2 has a low transmission rate [1, 2]. The human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) is a key target for the development of novel anti-HIV medicines. HIV-1 RT inhibitors are used to treat HIV infection as well as to prevent HIV-1 transfer from mother to child [3, 4].

The goal of atomic docking is to determine the official geometries that a ligand may achieve with a target whose position is known. Any docking method must fulfill three basic responsibilities: (1) determining the authoritative site; (2) placing the ligand on the authoritative location; and (3) determining the quality of interaction for a specific ligand-receptor combination. The molecular processes of resistance linked with a specific three-dimensional complex of RT and a small molecule can be explained using molecular modeling. This strategy could also be utilized to find novel drugs that are active against HIV-1 RT mutants [5, 6]. If a data collection of known medications is used to do the molecular docking technique, docking-based approaches can be effective for estimating the importance of mutations for HIV-1 resistance [7, 8]. In contrast to structure-property relationship analysis, which requires data on a collection of low molecular weight compounds and their impact on a specific protein, molecular docking can be performed provided data on at least one complex of protein-ligand (protein-low molecular weight drug) is available. Due to side effects and the development of medication resistance, an increasing percentage of people with HIV infection are unable to use currently approved anti-HIV therapies, including invert transcriptase and protease inhibitors.

MATERIAL AND METHODS

Protein preparation

The study used an X-ray diffraction-based crystal structure of the Y188c mutant HIV-1 reverse transcriptase with a resolution of 2.60 [9, 10]. The protein was found in the Protein Data Bank (PDB). 1JLF (PDB ID). The discovery studio application removed all water particles from all protein structures (Figure1). Protein was relegated and, at long last, the protein was saved. [11, 12] pdbqt format

Ligand preparation

The ligand structure was taken from the PubChem database (Figure 2) and optimized with 3D-geometry, and the two-dimensional structure of mulriflorenol was converted into a three-dimensional structure using the open Babel atom converter and saved in the PDB format for Docking compatibility. Energy is reduced and converted to the ligand. ligand.pdbqt files [13, 14]. pdb records to the ligand.pdbqt files.

Active site prediction

The official location of the protein or more frequently than not, a stash at the protein's surface, comprises buildups capable of substrate specificity that operate as proton benefactors or acceptors regularly. The key phase in a structure-based sedate plan is distinguishing proof and characterization of official location. Computational and written reports have set the official place apart. The cast distinguishes the changing geographical localization of the protein. To envision the official location, these servers methodically outfit the zone and volume at the plausible dynamic position of each take.

Docking protocol

The receptor lattices were built using 92x110x25 network focuses in XYZ with a network box centered within the run of 18.2716, -15.2718, 27.1045 co-crystallized after the protein and ligand were converted to PDBQT data. The protein and ligand for docking were chosen at that stage, and the program was executed. Positional root-mean-square deviation (RMSD) results were grouped and discussed by the result with the most ideal free vitality of the official. Biovia discovery studio was used to investigate the protein-ligand interaction. The yields were examined using their atomic surfaces and various bonds. As PNG records, the yields are spared.

RESULTS AND DISCUSSIONS

HIV-1 infection causes acquired immunodeficiency syndrome, which is a life-threatening condition in humans [15]. Because the condition affects an increasing number of people each year, it poses a severe health care challenge [16]. The main goal of AIDS treatment is to stop the virus from reproducing. Many studies have shown that HIV's viral reverse transcriptase is a multifunctional enzyme important for the virus's life cycle, making it an appealing target for anti-HIV medicines [17]. The mutation of HIV, which provides resistance to enzyme inhibitors, is a stumbling block in the treatment of AIDS (witch protease, integrase, and reverse transcriptase). The majority of currently available antiretroviral medications are extremely cytotoxic to patients [18]. As a result, including computational approaches for the planning of new medications is one of the tactics utilized nowadays in modern medical chemistry [19-20].

The heat atoms in the protein, such as water molecules and ligand groups, were removed and converted to an autodock compatibility file in PDBQT format for our investigation of the Y188c mutant HIV-1 reverse transcriptase. Multiflorenol, is a tiny molecule, with a minimum energy of 2630.83. Finally, the file was translated to PDBQT format and saved. TRP88, ALA158, VAL8, and PRO9 are residues found in the active areas of this protein, which were identified and described by the cast. They're also backed up by academic studies. The many protein conformations with each ligand were investigated. Baurenol and Multiflorenol had the best binding affinity of -8.1. H-bond distances and H-bond interaction residues were measured (Table 1). The root means square deviation value will be zero in those conformations. The binding affinity of those compounds with the macromolecule in various conformations, as well as the Root Mean Square Deviation (RMSD) values of the interacting molecules (Protein and Ligand), agreed (Table 2). Protein-ligand interactions (Multiflorenol) were studied (Figures 3, 4, 5, 6, 7, 8, and 9). It's also visible in charts like the Ramachandran plot (Figure 10) and the Hydrophobicity plot (Figure 11), as well as contact plots like the C-alpha plot (Figure 12), C-Beta plot (Figure 13), Sidechain plot (Figure 14), H bond plot (Figure 15), and Residue plot (Figure 16). (Figure 16). As a result, Multiflorenol is a promising HIV-1 treatment.

Table 1. The molecular docking studies of Multiflorenol with Y188c mutant HIV-1 Reverse transcriptase

S. No	Compound name	Docking score	H-Bond Interaction	Distance
1.	Multiflorenol	-8.1	TRP88 UNK1 ALA158 PRO9 VAL8	4.34 4.99 4.27 4.10 3.63 4.40 4.97

Table 2 shows the various binding affinity and root mean square deviation (RMSD) Upper and Lower Bound values of Multiflorenol

Ligand	Binding Affinity	rmsd / ub	Rmsd / lb
1jlf_A_multiflorenol_uff_E=2630.83	-8.1	0	0
	-7.8	19.685	15.097
	-7.7	2.159	1.538
	-7.7	6.979	2.569
	-7.5	4.18	1.933
	-7.4	44.741	41.675
	-7.4	7.621	2.586
	-7.2	7.609	2.69
	-7.2	29.984	26.909

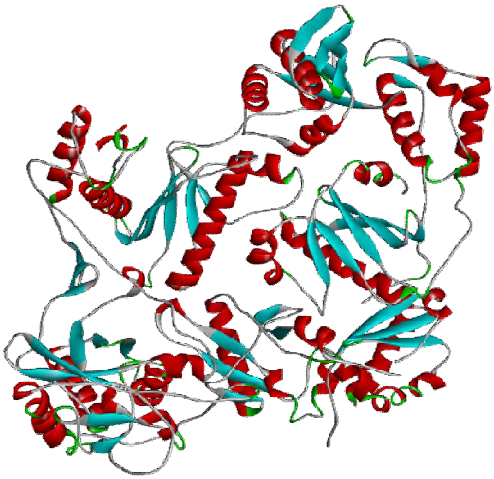

Figure 1 shows the 3D structure of Y188c mutant HIV-1 Reverse transcriptase

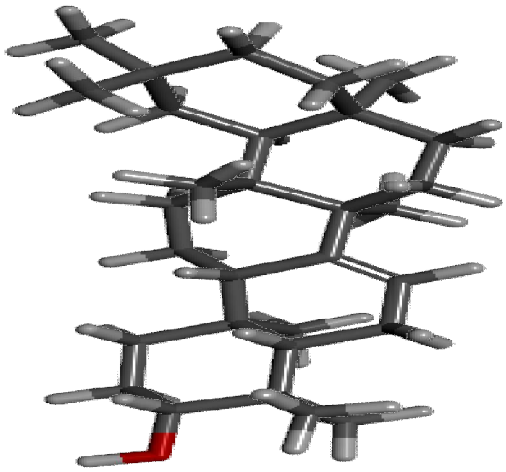

Figure 2 shows the 3D structure of Multiflorenol

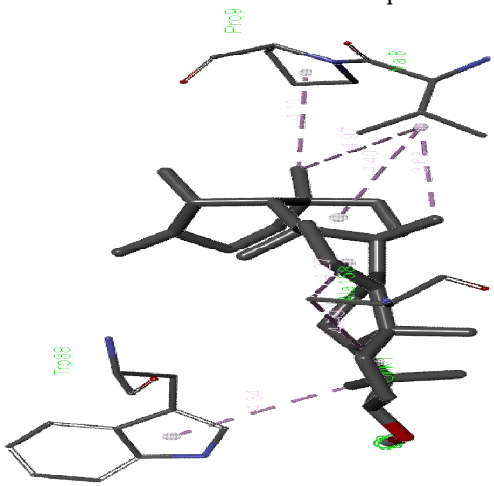

Figure 3 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase

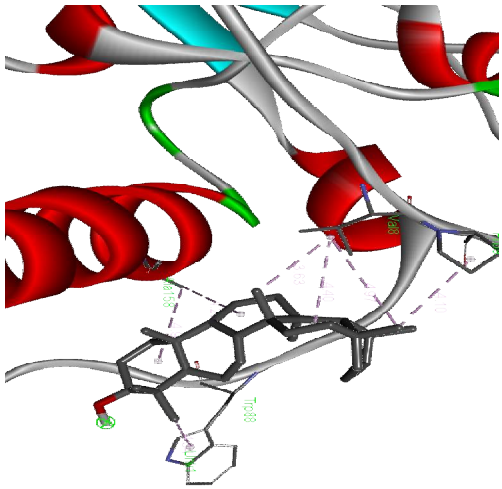

Figure 4 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase with their receptors

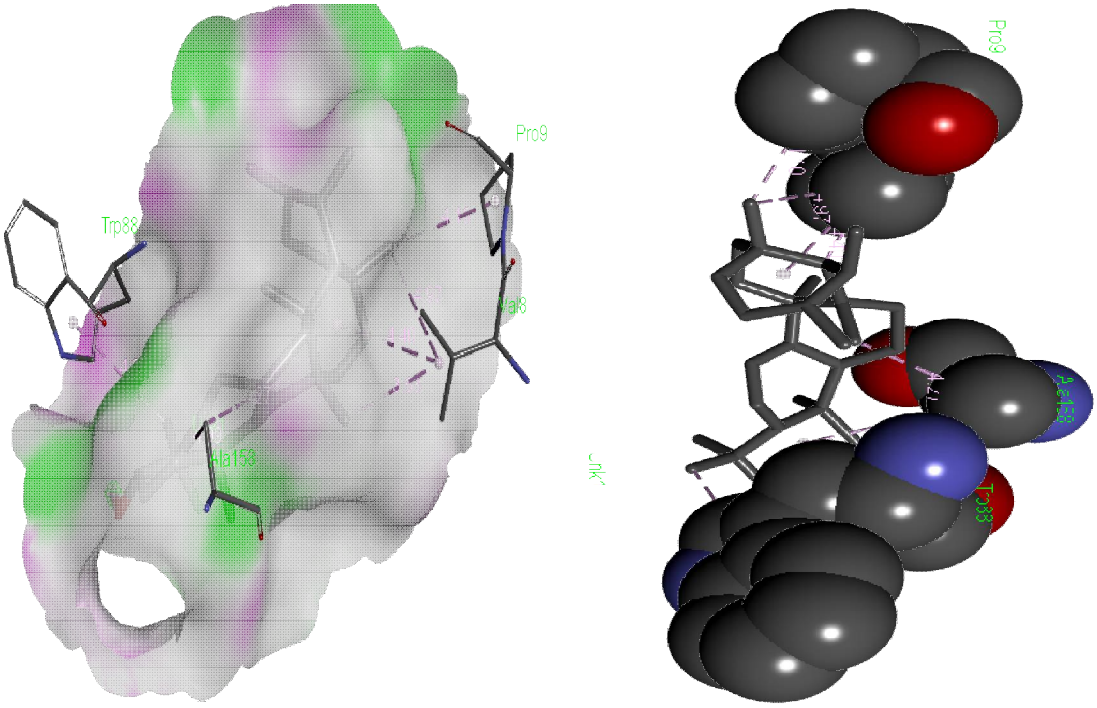

Figure 5&6 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase with their molecular surfaces

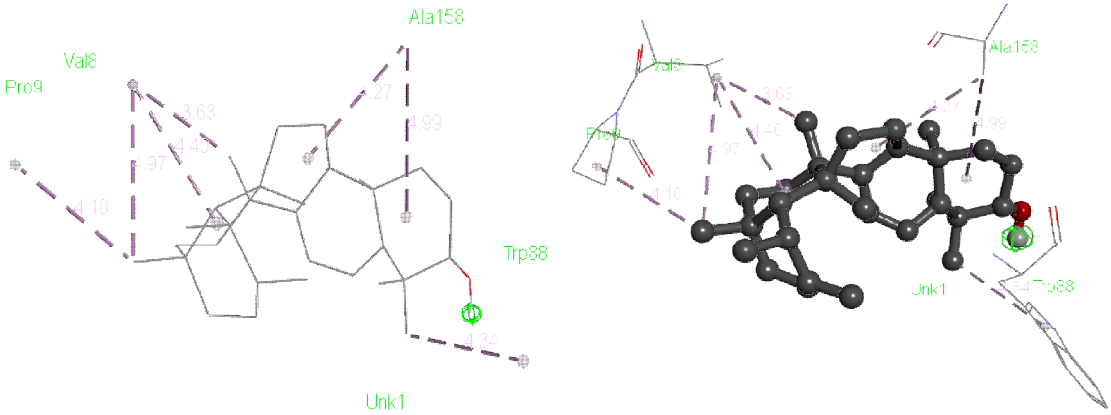

Figure 7, 8 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase with their bonds

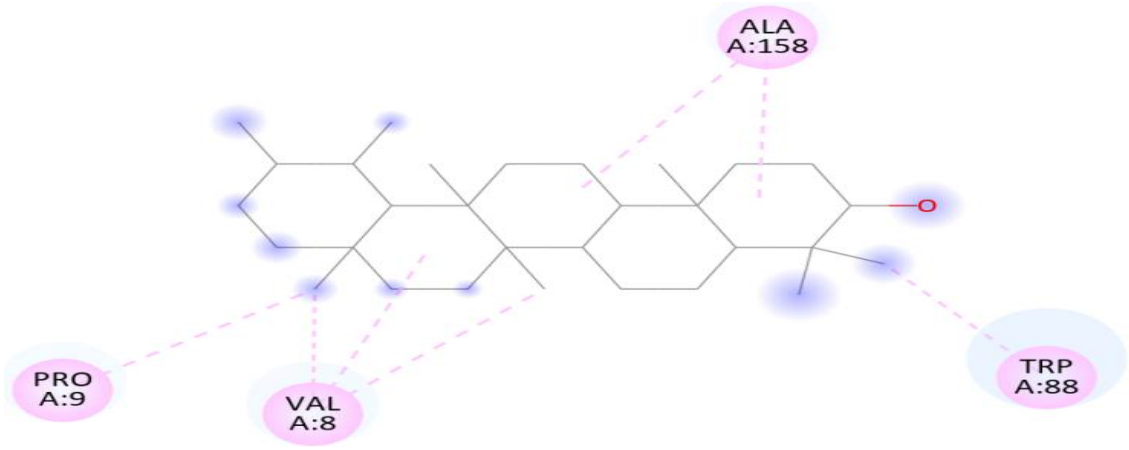

Figure 9 shows the 2d diagram of the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase with their bonds

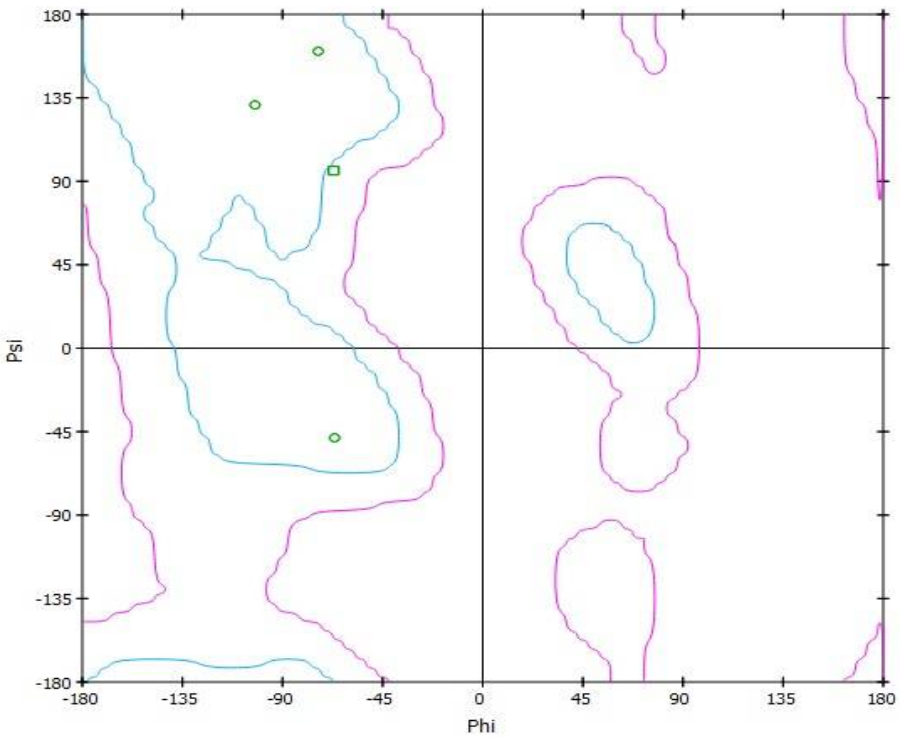

Figure 10 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase in Ramachandran Plot

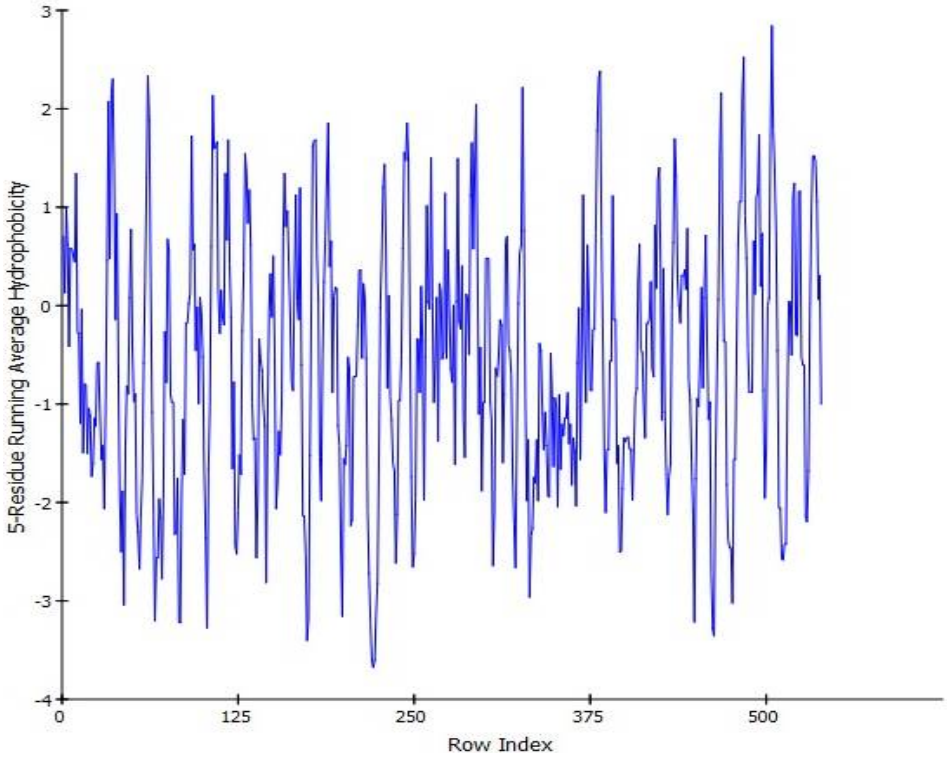

Figure 11 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase in Hydrophobicity Plot

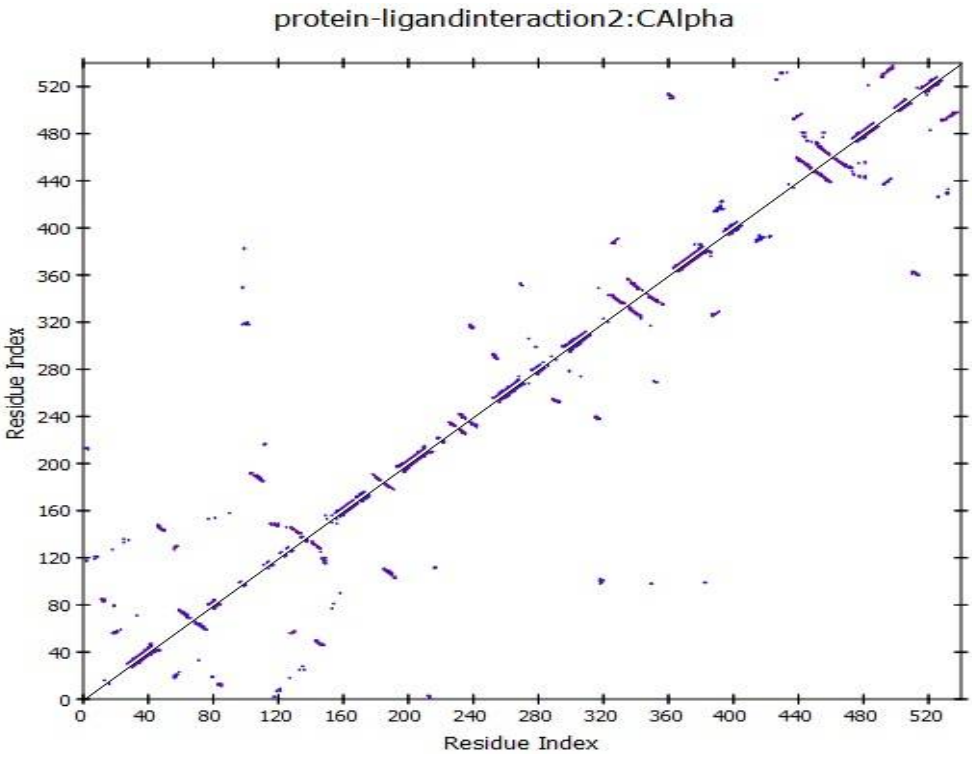

Figure 12 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase in C-Alpha Plot

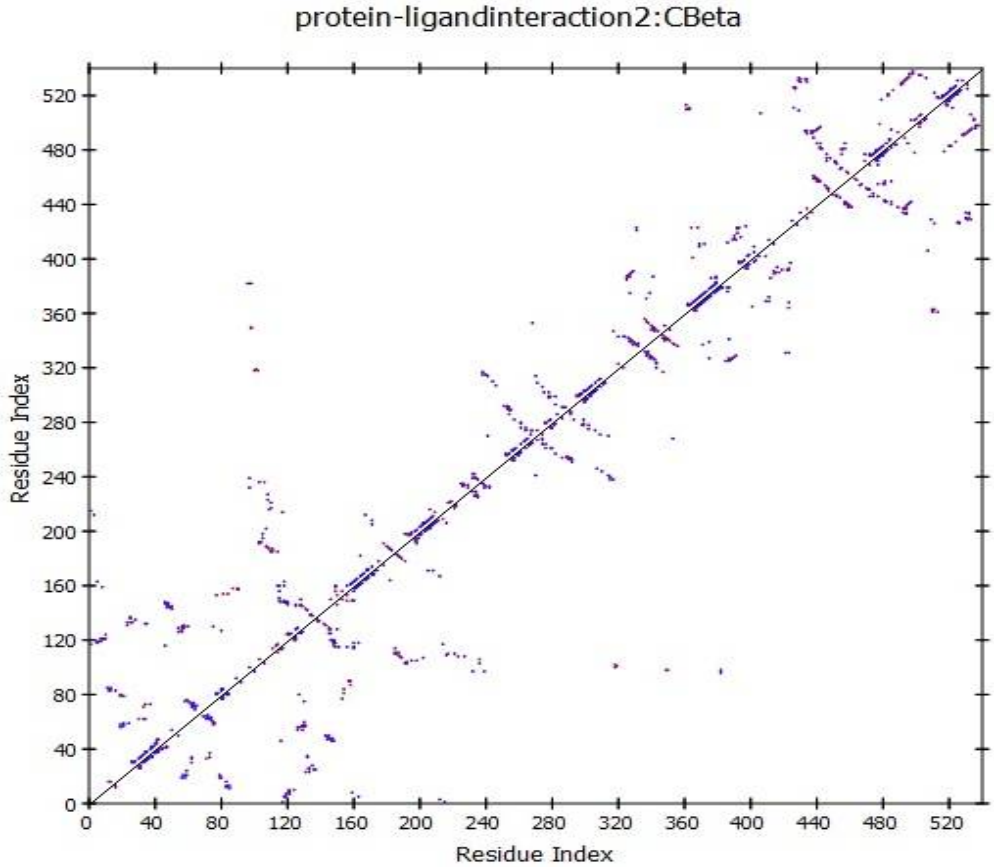

Figure 13 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase in C-Beta Plot

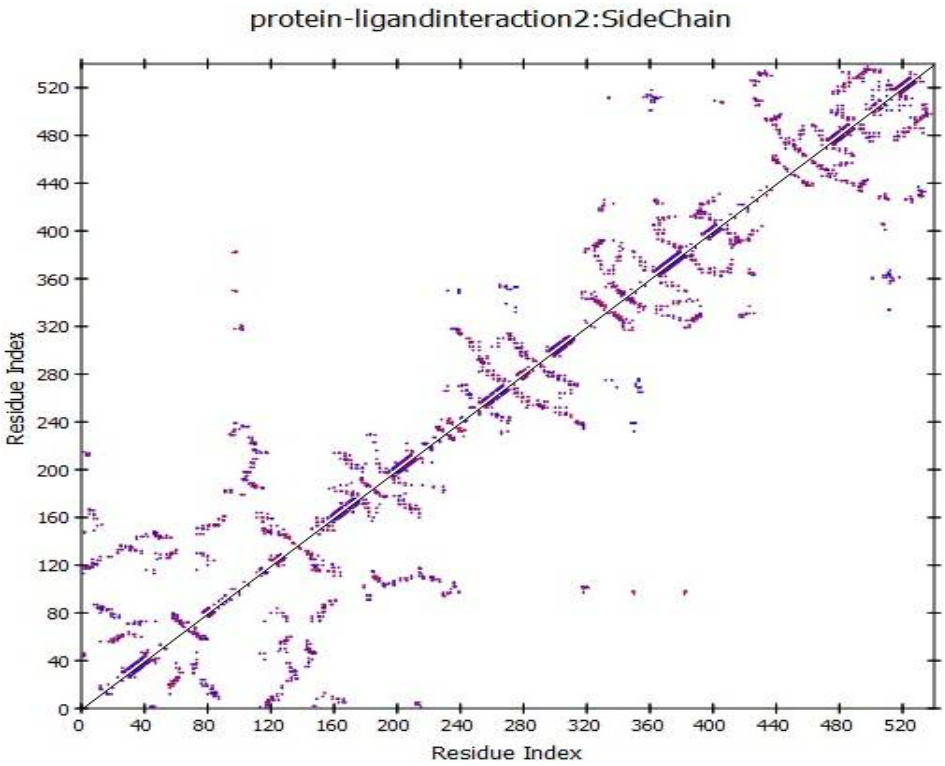

Figure 14 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase in Side chain Plot

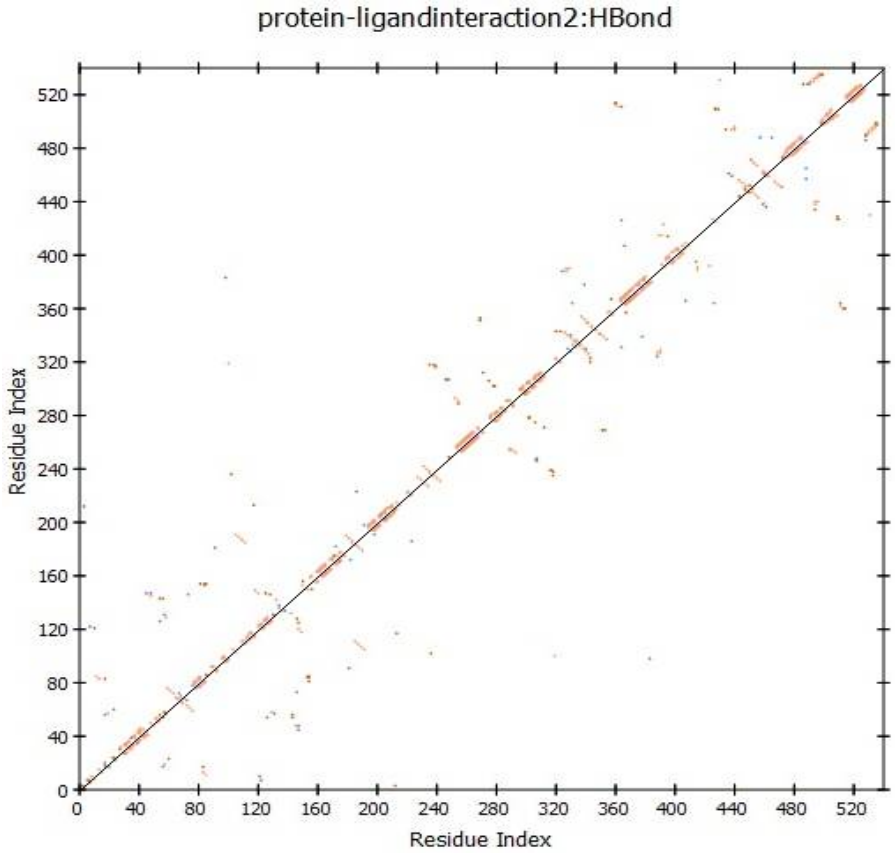

Figure 15 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase in H-bond Plot

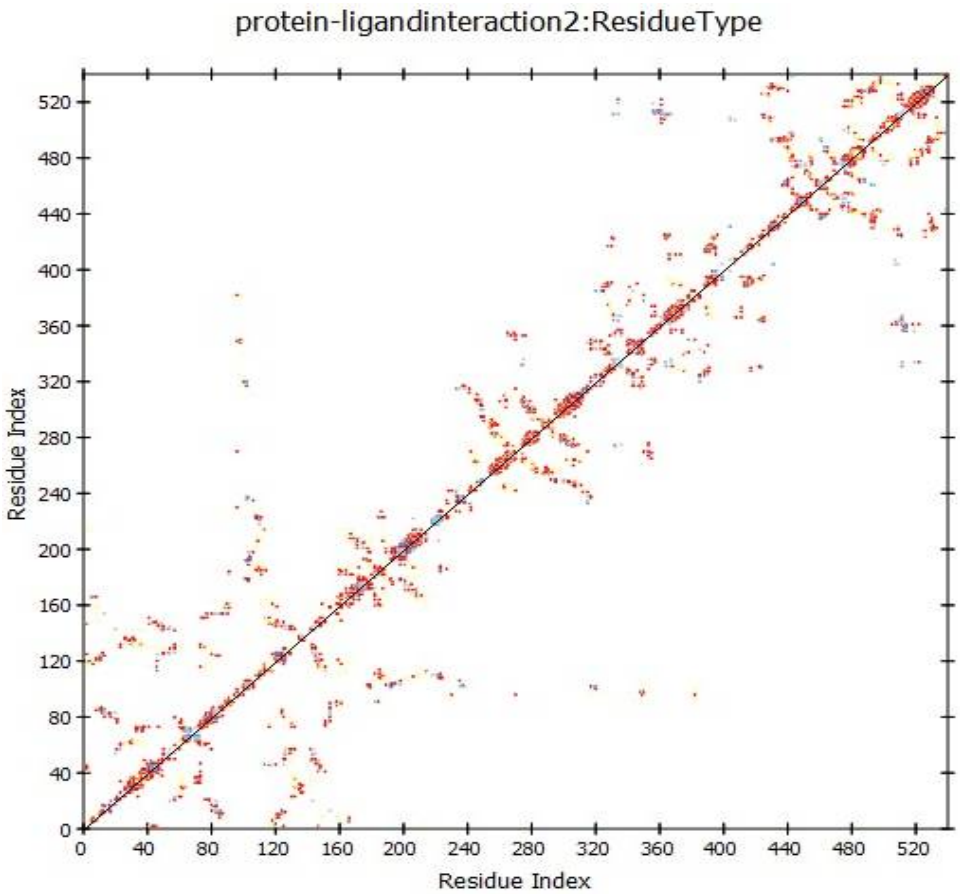

Figure 16 shows the interaction of Multiflorenol and Y188c mutant HIV-1 Reverse transcriptase in Residue Plot

CONCLUSION

Computational medicinal chemistry studies are being used to search for bioactive with the optimal multi-target interactions for HIV-1. Molecular docking investigations of representative compounds were done to better understand the binding mechanisms of inhibitors to the active site of HIV-1 protein. Those chemicals had the best binding affinity of -8.1. TRP88, ALA158, VAL8, and PRO9 are some of the most important residues that interact with HIV-1 RT. Various interactions, like the Ramachandran plot, can also be used to prove it. The tiny compounds are strongly linked to the HIV-1 RT protein that is being studied. As a result, they could be effective antiretroviral medicines.

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