IJPSR (2021), Volume 12, Issue 2 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 March 2020; received in revised form, 11 June 2020; accepted, 14 August 2020; published 01 February 2021

MOLECULAR MODELLING OF HIV-1 DRUG RESISTANT MUTANTS WITH REFERENCE TO WILD TYPE

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Keywords:

HIV, AIDS, Tenofovir, Lamivudine, Efavirenz, Nevirapine, Molecular docking

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ABSTRACT: Drug resistance mutations M184V and M184I are associated with lamivudine. Y181C and H221Y drug resistance mutations are associated with nevirapine and efavirenz and G190R and M230I drug resistance mutations are associated with efavirenz in the reverse transcriptase gene of HIV-1. In the present study, we attempted to identify the drug resistance mutations and interacting amino acids in the reverse transcriptase gene of HIV-1 through a molecular docking approach. Molecular docking of first-line antiretroviral drugs like lamivudine, nevirapine, and efavirenz with wild and mutant type structures was performed using MTi auto dock to compare the binding behaviour of drugs with amino acids of the reverse transcriptase gene. The receptor structure preparation was performed by the University of California, San Francisco chimera (UCSF Chimera). The Ligplot program was used to plot the 2D interaction diagrams of protein-ligand complexes. The 3D models of the mutant-drugs were generated using PyMOL (PyMOL molecular graphics system). The clear bond interactions were visualized with Discovery Studio 3.5 (BIOVIA, USA). Thus, these findings suggest that mutations in the reverse transcriptase gene, thereby leading to drug resistance in HIV-1 infected patients due to the incompetent binding of the drugs.

INTRODUCTION: The human immuno-deficiency virus (HIV) causes a syndrome called acquired immunodeficiency syndrome (AIDS).

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(2).1263-71

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(2).1263-71

The spreading of HIV strains in the human population acquired at the time of treatment and leads to drug resistance [1].

The over-spreading of drug-resistant mutants are a serious problem in a public health concern. The study of drug-resistant mutants was very important during the treatment of antiretroviral therapy (ART) [2]. The drug resistance study is a good clinical practice for HIV-infected patients, which treated with first line ART.

During the treatment of first-line ART, two nucleotide / nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor's (NNRTIs) were recommended. The Genotypic test is the only way to find out resistance mutations towards NRTIs and NNRTIs in HIV-infected patients [3]. The protease (PR) and reverse transcriptase (RT) of HIV is reported as the main target for drug discovery. Molecular docking is a method of drug discovery. Molecular docking is a computational method used to identify medicines for HIV [4]. The dual inhibitors of HIV reverse transcriptase and integrase were screened for synthesis and biological testing through a molecular modelling approach [5]. The polymerase gene of HIV-1 was played main role in virus replication.

The action of the reverse transcriptase gene of the polymerase of HIV-1 drug resistant mutants was studied using molecular modelling method [6]. Anti-HIV drugs could not compete for the rapid emergence of HIV-1 drug-resistant variants. Computational methods are a significant approach to screen the number of reverse transcriptase inhibitors for several drug resistant isolates [7].

Thus, we focused on nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors associated with HIV-1 drug-resistant mutants. In this study, molecular modelling was performed for M184V, M184I, Y181C, H221Y, G190R and M230I mutants using the HIV-1 wild type as a reference strain.

METHODS:

Modelling of Mutant Structures: Modelling of the mutant's structure was performed using SWISS-MODEL [8-9]. PyMol was used to change the amino acid residue at the specified position in the wild type HIV-1 RT sequence (PyMol, USA). For the prediction of mutant structures, the wild-type sequence of HIV-1 RT (PDB ID: 1IKW) was used as a template and validated through PROCHEK analysis [10].

Docking Study of Wild Type and Mutant Structures with Drugs: Molecular docking of first-line antiretroviral drugs (lamivudine, nevirapine, and efavirenz) with wild and mutant type structures was performed to compare the binding behaviour of drugs with amino acids of the reverse transcriptase gene. Receptor structure preparation was performed by the University of California, San Francisco chimera (UCSF Chimera) [11]. MTi Autodock was used for molecular docking [12]. The ligplot program was used to plot the 2D interaction diagrams of protein-ligand complexes [13]. The 3D models of the mutant-drugs were generated using PyMOL (PyMOL molecular graphics system), and clear bond interactions were visualized using Discovery Studio 3.5 (BIOVIA, USA).

Molecular Docking of Wild Type and Mutants with First-line Anti-retroviral Drugs: To evaluate the conformational changes of these mutations with respect to the Lamivudine, Nevirapine, Efavirenz and molecular docking was performed and the binding energy was calculated.

Molecular Docking of Lamivudine Complexes with the Reverse Transcriptase M184V/I Mutant: We compared the crystal structure of the wild-type with an HIV-1 RT mutant (M184V) by docking studies. The docking structure of the wild-type RT-ligand and M184V mutant ligand complex revealed an adequate difference between these two types.

In RT-Lamivudine wild type complex, amino acids like Tyrosine271, Glutamine242, Proline243, Valine241, Leucine310, Lysine311, and Valine245 were involved in hydrophobic interaction with lamivudine. The β-branched amino acids Valine241, Leucine310, and Valine245 of wild - type RT were involved in hydrophobic interactions with lamivudine in the RT-Lamivudine wild-type complex, but the β-branched amino acid Ile 244 interacted with an OH group of lamivudine through the hydrogen bond in the bond length 2.74 A^0. Pi-cation interactions were observed in Ile 244 with the backbone of lamivudine. The amino acids Proline 243 and Proline313 were involved in the Vander Waals interaction.

In the docking structure of the RT mutant type (M184V)-lamivudine complex, the RT backbone amino acids Isoleucine 244 and Tyrosine 271 were involved in an interaction with lamivudine through hydrogen bonds with a bond length of 2.72A^0 and 2.93A^0. The amino acids Lysine 311, Proline313, and Glutamine 242 were involved in the Vander Waals interaction with lamivudine. The RT wild-

type lamivudine binding energy was -5.940 kcal/mol, whereas the RT mutant M184V-Lamivudine was -6.49 kcal/mol.

In addition, this type of docking model was generalized to explain the RT resistance to all nucleoside inhibitors with B-L stereochemistry. The wild-type and mutant model will be helpful in implications in drug design.

The docking study of the RT mutant M184I-Lamivudine complex, the amino acids Serine162 and Glutamine161 were involved in an interaction with lamivudine through hydrogen bonds. The hydrogen bond lengths of 2.93A^0 and 2.80A^0 were observed. The amino acids Lysine166, Valine90, Proline52, and Proline140 were involved in hydrophobic interactions with lamivudine. The amino acids Lysine49, Isoleucine142, Lysine166, and Proline140 were involved in the Vander Waals interaction with the lamivudine.

From the docking study in the reverse transcriptase gene of HIV-1, we suggested that the mutation in the 184 position affects the amino acid-binding of the entire RT gene with lamivudine. The positional amino acid changes in the RT gene of HIV-1 affect lamivudine binding during therapy.

The details of the 2-D view were given in **Fig. 1(a), 1(b), 1(c)** and the 3-D view is given in **Fig. 2(a), 2(b)** and **2(c)**.

The details of the above discovery studio structure are given in the supplementary **Fig. 1, 2,** and **3**.

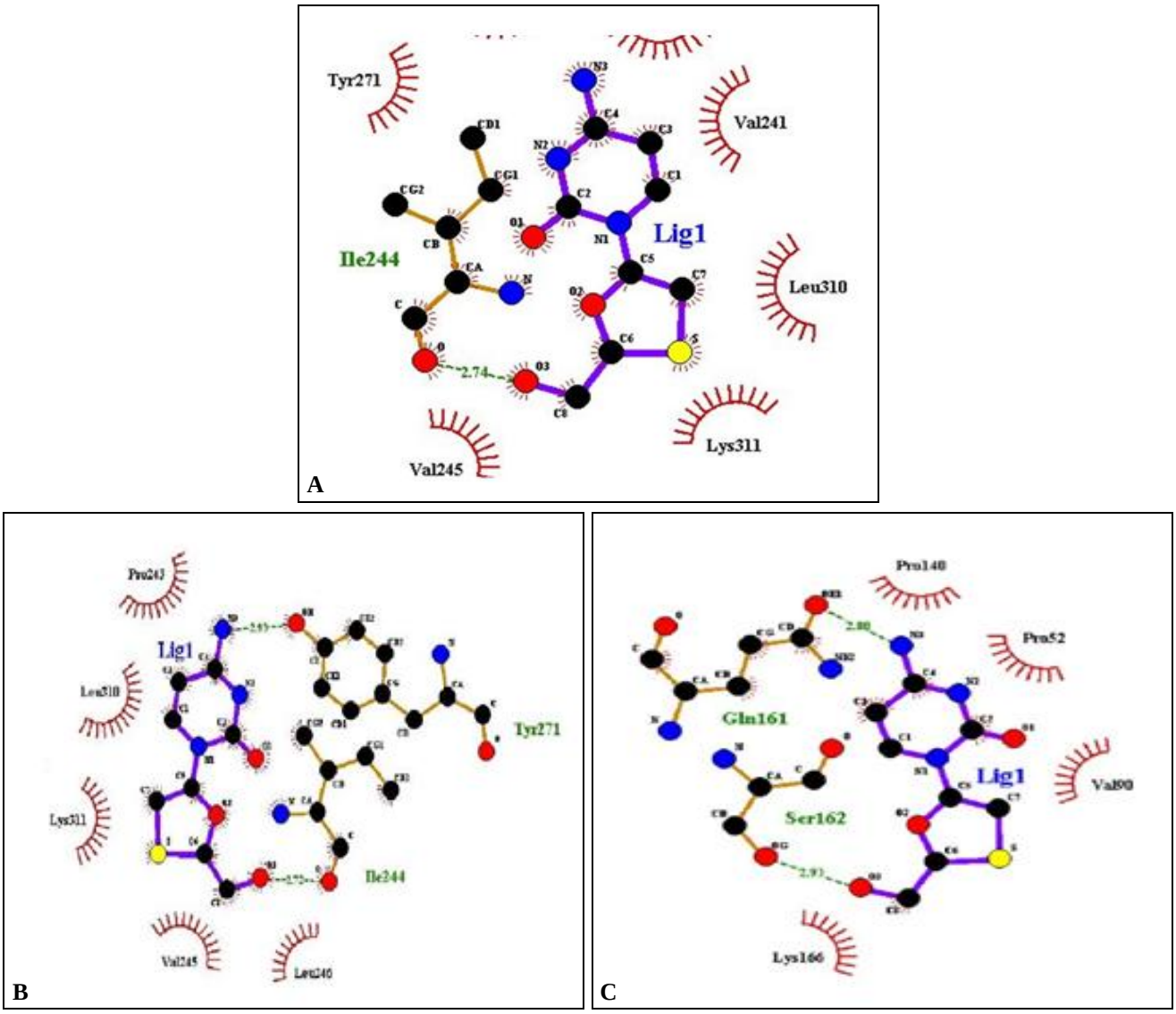

FIG. 1: 2D VIEW: 1A RT WILD TYPE-LAMIVUDINE COMPLEX, 1B: RT M184V MUTANT LAMIVUDINE COMPLEX, IC: RT M184I MUTANT LAMIVUDINE COMPLEX

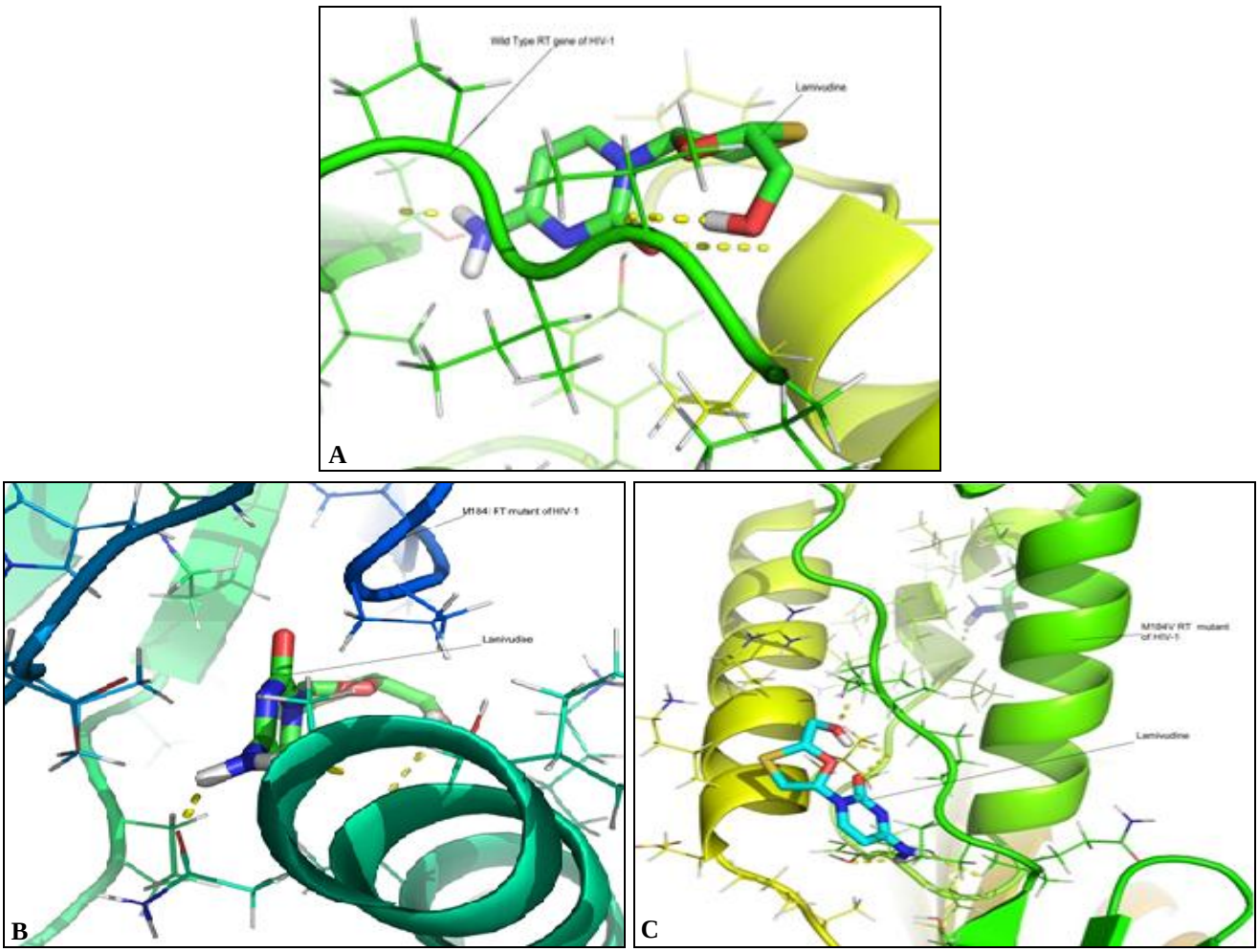

FIG. 2: 3D VIEW: 2A RT WILD TYPE-LAMIVUDINE COMPLEX, 2B: RT M184V MUTANT LAMIVUDINE COMPLEX, 2C: RT M184I MUTANT LAMIVUDINE COMPLEX

Molecular Docking of Nevirapine/Efavirenz Complexes with Y181C, H221Y and G190R M230I RT Mutants of HIV-1: In the docking structure of the RT wild-type-Nevirapine complex, the RT backbone of the two amino acids at positions 167 and 168 were involved in hydrophilic interactions with nevirapine. The RT backbone amino acids Tyrosine188, Tyrosine181, Leucine 100, Valine179, Glycine198, Lysine101, Proline 236, Histidine235, Val106, Tyrosine 318, Phenyle 227, Tryptophan229 and Leucine234 were involved in the hydrophobic interaction with nevirapine.

Tyrosine188 and Tyrosine181 is involved in Pi-bond interactions between the aromatic ring of the nevirapine.

In the RT mutant type (Y181C and H221Y)-Nevirapine complex, no hydrophilic interactions were observed in the RT backbone amino acids. The RT backbone amino acids Cystine181, Tyrosine188, Tryptophan229, Phenylalanine227, Leucine234, Leucine100, Tyrosine318, Valine106, Glycine190, Valine179 and Valine189 were involved in hydrophobic interactions with nevirapine.

Tyrosine 188 was involved in the Pi interaction with the aromatic ring of the nevirapine. Cystine181 was involved in the electrostatic interaction with nevirapine. The docking structure of the RT wild type-Efavirenz complex, the RT backbone amino acid Lysine101 interacted with the aromatic ring of efavirenz with a bond length was $2.75A^0$. The amino acids Lysine103, Proline236, Tyrosine318, Hisdine235, Tyrosine181, Valine106, Leucine234, Tyrosine188, Tryptophan 229, and Leucine100 were involved in hydrophobic interactions with efavirenz. The amino acids Proline236, Valine179, Tyrosine318, Lysine103, Leucine100, Leucine234, Phenyl alanine227, Valine106, Proline225, and Histidine235 were involved in Vander Waals interaction with efavirenz.

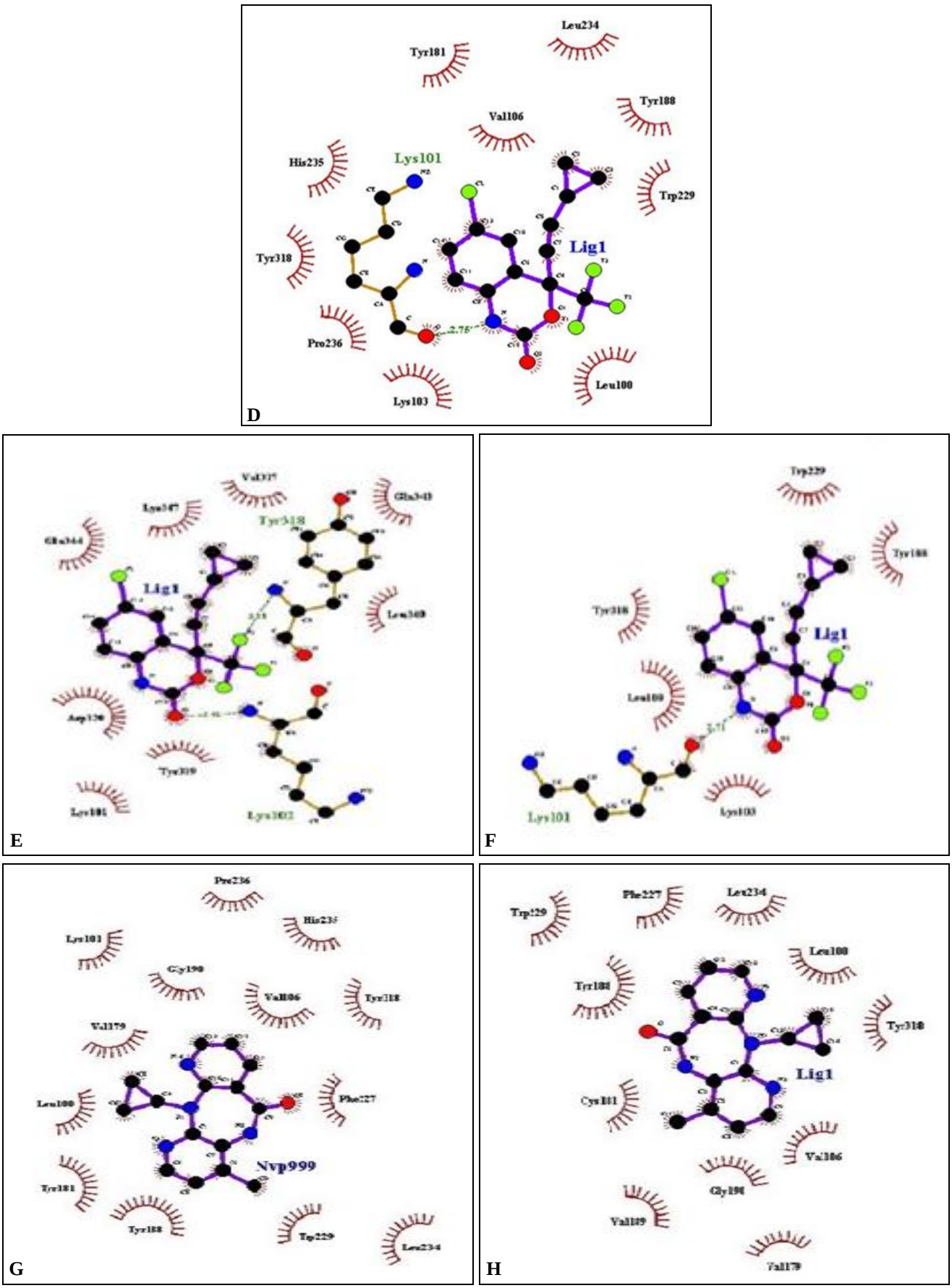

FIG. 3: 2D VIEW: 3(D): RT WILD TYPE-EFAVIRENZ COMPLEX, 3(E): RT G190R AND M230I MUTANT-EFAVIRENZ COMPLEX, 3(F): RT Y181C AND H221Y MUTANT-EFAVIRENZ COMPLEX, 3(G): RT-WILD TYPE-NEVIRAPINE COMPLEX, 3(H): RT Y181C AND H221Y MUTANT-NEVIRAPINE COMPLEX

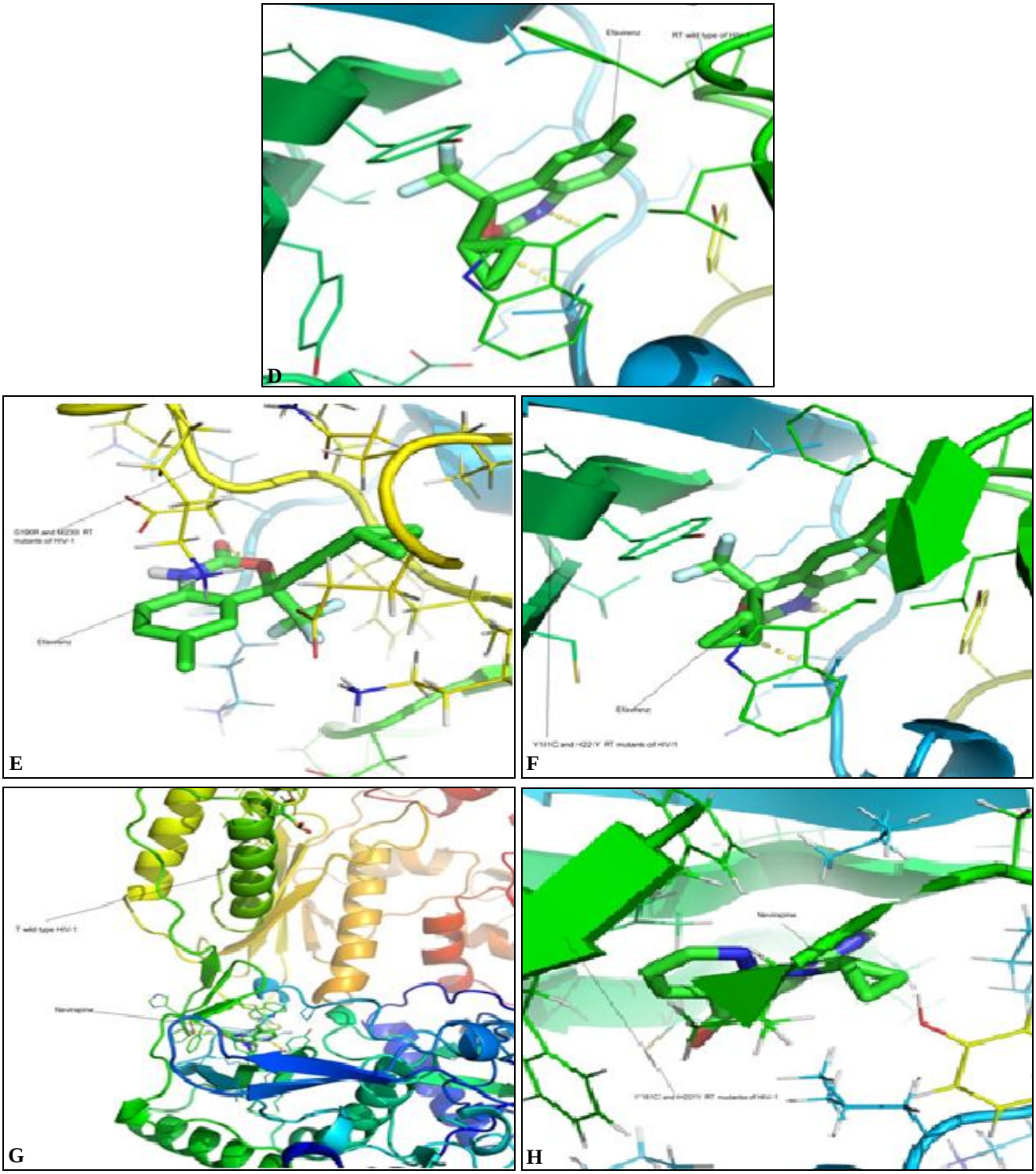

FIG 4:3D VIEW: 4(D): RT WILD TYPE-EFAVIRENZ COMPLEX, 4(E): RT G190R AND M230I MUTANT-EFAVIRENZ COMPLEX, 4(F): RT Y181 C AND H221Y MUTANT-EFAVIRENZ COMPLEX, 4(G): RT-WILD TYPE-NEVIRAPINE COMPLEX, F4(H): RT Y181C AND H221Y MUTANT-NEVIRAPINE COMPLEX

The amino acids Lysine102, Lysine101, Glycine190, Tyrosine181, and Tyrosine188 were involved in electrostatic interactions with efavirenz.

In the docking study of RT mutant types Y181C and H221Y-Efavirenz complex, the Lysine101 interacted with the aromatic ring of Efavirenz in a bond length 2.71A^0. The amino acids Lysine103, Leucine100, Tyrosine318, Tryptophan229, and Tyrosine188 were involved in hydrophobic interactions with efavirenz. The amino acids Lysine101, Lysine102, Tyrosine188, and Glycine 190 were involved in electrostatic interaction with Efavirenz. The amino acids Valine179, Leucine

100, Cystine181, Trptophan229, Lysine103, Leucine 234, Histidine235, Proline225, Proline236, Phenyalanine 227, Tyrosine31 andValine106 were involved in the Vander Waals interaction with efavirenz.

The docking study of this NNRTI drug resistance in clinical isolates can exploit these observations to design more effective drugs, strategies of drug administration, and highlight their mechanisms of action more efficiently. The binding energies of the RT mutant type (Y181C and H221Y)-Nevirapine complex were -6.70 kcal/mol, and the binding energy of the RT mutant type (Y181C and H221Y)-Efavirenz complex was -8.95 kcal/mol. The docking study of RT wild type-Efavirenz complex highlighted the hydrophilic interaction of Lysine 101 with lamivudine and was shown to have a 2.75A^0 bond length between the oxygen atom of lysine and the nitrogen atom of lamivudine.

The amino acids Lysine103, Proline236, Tyrosine 318, Hisdine235, Tyrosine181, Valine106, Leucine 234, Tyrosine188, Tryptophan229, and Leucine100 were involved in hydrophobic interactions with lamivudine. But in a docking study of the RT mutant (G190R and M230I) with the Efavirenz complex, the amino acid Lysine 102 interacted with the aromatic ring of the lamivudine with the bond length of 2.91A^0.

The amino acid Tyrosine318 was involved in the side-chain aromatic ring of lamivudine with a bond length of 3.11A^0. The RT backbone amino acids Lysine101, Tyrosine319, Aspergine320, Glutamine 344, Lysine347, Valine317, Glutamine343, and Leucine349 were involved in hydrophobic interactions with lamivudine. Lysine 323 is involved in Pi-bond interaction with the aromatic ring of efavirenz. Lysine 347, Asparagine 320, Tyrosine 319, Lysine 102, Tyrosine 318, and Asparagine 237 were involved in electrostatic interaction with the efavirenz. The amino acids Lysine101, Proline321, Valine317, Leucine349, Lysine323, Glutamine343, and Glutamine344 were involved in Vander Waals interactions with efavirenz.

The binding energies of the RT mutant type G190R and M230I efavirenz complex was-7.04 kcal/mol. The details of the 2-D view are given in **Fig. 3(d), 3(e), 3(f), 3(g), 3(h)** and in 3-D view in the **Fig. 4(d), 4(e), 4(f), 4(g)** and **4(h)**. The above discovery studio structure is given in supplementary **Fig. 4, 5, 6, 7** and **8**.

DISCUSSION: HIV drug resistance is the ability of HIV to mutate and reproduce itself in the presence of antiretroviral drugs. The outcome of this HIV drug resistance leads to treatment failure and further spread of drug-resistant HIV. This scenario ultimately can compromise the effectiveness of the limited therapeutic options. To overcome this situation, proper planning for regimen selection should be prioritized through mutation-guided regimen approach. Lamivudine has been shown to be highly effective in the treatment of HIV-infected patients. A single mutation at amino acid position 184 changes to Valine and confers resistance to Lamivudine [14, 15.]

The novel idea of drug-nucleotide interaction on a specified position of mutation and showed the novelty of interaction that can favor a suitable drug binding on the specific position of the reverse transcriptase region of HIV-1 [16]. Treatment with a combination of antiretroviral therapies has resulted in a dramatic decrease in mortality due to AIDS. The 2', 3'-dideoxy-3'-thiacytidine (3TC Lamivudine) is a nucleoside reverse transcriptase inhibitor.

Resistance to lamivudine was associated with the substitution of Isoleucine to Methionine at position 184 of HIV-1 reverse transcriptase, which brought a single base change (ATG to ATA). During the lamivudine treatment, the M184I variant is replaced by the variant M184V. Lamivudine inhibits reverse transcriptase by terminating the growing DNA chain. In the above docking results, we compared the binding energy of HIV-1 wild type and mutants; we observed a decrease in the binding energy between the lamivudine and M184V/I reverse transcriptase gene mutant of HIV-1. Thus, we concluded that mutation in the 184 position lowers the binding energy to reject the drug binding in the RT gene of HIV-1.

For RT Lamivudine mutants at positions M184V and M184I, we found that Isoleucine and Valine were involved in intermolecular and hydrophobic interactions with lamivudine. These two amino acids are involved in steric hindrance with the side chain of lamivudine. In a previous study, the fitness of these genotypically altered viruses was selected through drug pressure by giving nevirapine

treatment, and the nevirapine resistance mutations were analyzed [17]. The docking study of H221Y with efavirenz/ nevirapine could be a new idea or novel approach to design a more effective drug substitute for NNRTI to suppress the H221Y mutation as the arrangement of amino acids was revealed.

Nevirapine inhibits the reverse transcriptase activity and replication mechanism of HIV-1 through noncompetitively binding to the conserved tyrosine residues at 181 and 188 of the p66 subunit of the RT gene [18, 19]. The Nevirapine resistant virus contains a tyrosine to a cysteine mutation at residue 181 that is cross-resistance to other non-nucleoside reverse transcriptase inhibitors [20]. The novel mutations L74V and H221Y frequently, often with Y181C, share its ability to increase NNRTIs resistance mutations [21].

According to Stanford University DataBase, H221Y is a non-polymorphic accessory NNRTI mutation that occurs in combination with Y181C and has minimal effect on NNRTI susceptibility. H221Y it does not decrease susceptibility. This may contribute to the decrease in NNRTI susceptibility in combination with other NNRTI.

The structurally predicted nevirapine/efavirenz mutations observed in our study might give us lead to the design of competitive drug molecules that can bind to the reverse transcriptase gene of HIV and inhibit virus replication in the human host. The crystallographic structure of H221Y with NNRTI have not yet been reported. A lower in binding energy was observed in the Y181C and H221Y mutants compared to the wild type was observed. From the above docking study of Y181C and H221Y mutants, we observed that two NNRTI drugs uncompetitively bind to the RT gene during the replication cycle leads to treatment failure. Thus, the binding energy could have an impact on chain synthesis during virus replication.

The molecular mechanism and crystallographic study of M230I and G190R mutations with NNRTI binding have not yet reported. There is no reported evidence about the molecular mechanisms of Nevirapine/Efavirenz binding in M230I and G190R RT mutants. Our docking study provided the structural information on various types of amino acids involved in the M230I and G190R RT mutants of HIV-1.Overall, the molecular docking of the various drug-resistant mutants towards first-line antiretroviral drugs provides suitable information on NRTI and NNRTI drug design that can work even the mutation occurs in a specified position.

CONCLUSION: The docking study and structural prediction of these mutations by computational approach would be helpful in new drug discovery in HIV research.

PMDB Accession Number: The docking structure of drugs and mutations were submitted to a protein model database and were assigned in the following id: PM0081676, PM0081677, PM0081678, PM00-81680, PM0081681, PM0081682, PM0081683, and PM0081945.

ACKNOWLEDGEMENT: Indian Council of Medical Research, New Delhi, India supported Sushanta Kumar Barik by senior research fellowship (File no. 80/990/2015-ECD-I). Dr. Bhawna Sharma is acknowledged for reviewing the manuscript for the English language.

FUNDING: Indian Council of Medical Research, Govt. of India, New Delhi.

CONFLICTS OF INTEREST: We do not have any conflict of interest.

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How to cite this article:
Barik SK, Singh D, Mohanty PS, Tripathy SP, Jena S, Dwivedi VD and Mohanty KK: Molecular modelling of HIV-1 drug resistant mutants with reference to wild type. Int J Pharm Sci & Res 2021; 12(2): 1263-71. doi: 10.13040/IJPSR.0975-8232.12(2).1263-71.