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HIV-1 CA Inhibitor Capacity of Different Derivatives of di-Pyrrole Benzene

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Abstract

Introduction: Modelling of cost effective HIV drug is one of the major research area in the field of drug designing. Presently is observed that HIV-1 capsid assembly (CA) inhibitor drugs are mutation resistant. Thus, modelling of HIV drugs of this class with small organic molecules is the prime focus of present research work.

Methodology: It is very important that before experiments, in-silico drug test not only reduce the cost of experiments but also the time. Thus, in-silico drug tests are performed with our modelled compounds using molecular docking method.

Results: We found that our compounds, p-di-pyrrole benzene and its derivatives, show HIV-1 CA inhibitor activity in the micro-molecular level. We also computed and reported the LogP, charged surface area and binding properties of our compounds with the HIV-1 CA protein in the present article.

Conclusion: From our present study we may conclude that small organic molecules like p-di-pyrrole benzene and its derivatives are very good HIV-1 CA inhibitors. Thus, these compounds may be promoted for in-vivo and clinical tests.

Keywords: HVI-1 CA inhibitors, Molecular docking, QCM, P-di-pyrrole benzene.

Background

In very recent years, in-silico drug designing research area has grown in a rapid pace. It reduces the time and cost of drug designing by eliminating the unsuccessful trials. Several methods and computational packages are developed so far, for in-silico drug designing e.g., Quantitative Structure Activity Relationship (QSAR) method [1-5], molecular docking methods [6-9], Quantum computational methods (QCM) [10-16], molecular dynamic study [17-20], etc. Among all these methods QSAR based methods are most popular and wildly used for in-silico drug designing in the academic laboratories as well as in the industrial branches. On the other hand, molecular docking based methods and QCM are mostly used in academic laboratories. QCM is developing. Though, these methods are very accurate and required minimal data, we are unable to use these methods because there is no freely available web based packages. We used molecular docking methods for our calculations with the help of DOCKING SERVER [21] which is freely available in the web.

HIV is one of the epic diseases till at the beginning of the third decade of twenty first century when science and technology have developed

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Table 1: Computed binding constants of different compounds with HIV-1 CA protein.

Compounds	Binding Constant (Ki)	Binding frequency	H-bonding amino acids
Compound-1	18.09 Micro mole	30%	LEU116, THR117, GLU155, ALA175
Compound-2	17.8 Micro mole	30%	GLU155, ALA175
Compound-3	62.59 Micro mole	40%	GLU155, ALA175
Compound-4	34.22 Micro mole	10%	GLU155, ALA175

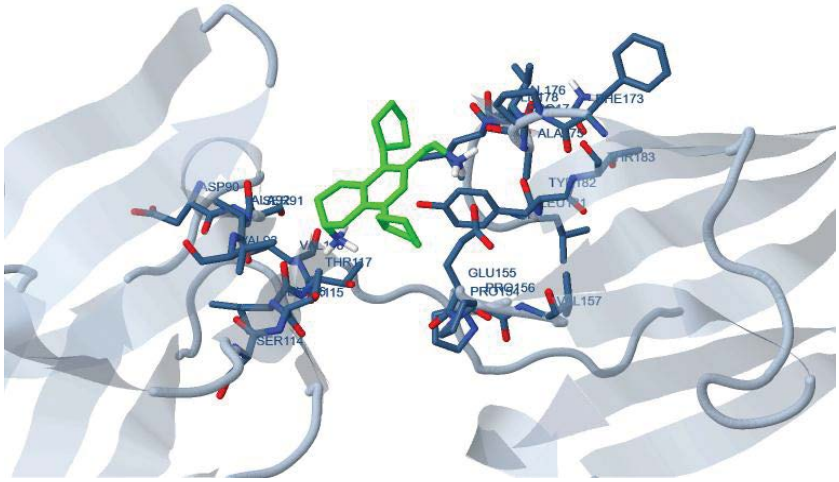

Figure 1: Docked Structure of Compound-1.

almost in all respect, automation is not only implemented in the computations but also in all areas of our daily life, robotics is extended to design human robot which is indistinguishable from an alive human. The dynasty of HIV is rapidly increasing rather decreasing. This is due to the anecdotal mutation capacity of HIV viral protein against any drug. Not only that, there are cross drug resistance which also rapidly developed by HIV virus when proper combination of drugs are not used for treatment. As a result, a major part of present research is focused on HIV drug discovery [22-30].

Presently, it is reported that HIV-1 Capsid Assembly (CA) protein which plays an important role in the recombination process of small genomes to form a cone shaped viral capsid has no capacity of drug resistant against any drug [31]. This is probably due to the energy minimal configuration and combination of amino acids at all three binding sites of CA protein of HIV. The mutation at any binding site is not related to decrease in inhibition capacity irrespective of the nature and size of the inhibitor. At the same time the viral fitness also decreases due to any kind of mutation. Thus, designing of HIV-1 CA inhibitor drugs would be a great idea for fight against HIV. In the present research work we have focused on it. Cost effectiveness of preparation and production of the proposed drug is another important issue. Thus, we planned to design small common organic compounds following a recent work by Bishwas et. al. [32].

Methods

We used Docking Server [21] for our calculation regarding the evaluation of binding constant of the modelled compounds with the HIV-1 CA protein. For these calculations we have taken HIV-1 CA protein structure from protein data bank which has the PDB ID as 1e6j. Auto Dock tool is used for docking. Standard docking parameters are used which are same as reported in reference 32. Gasteiger partial charge is added to all ligand compounds.

Results and Discussion

Simulated results are presented in table-1. It is observed that compound-1 and compound-2 have almost equal binding capacities as well as the binding frequencies. But, compound-3 has better binding frequency though its binding constant is higher compared to compound-1 and compound-2. It is known that lesser the binding constant higher is its inhibition capacity. Thus, compound-1 and 2 are the better inhibitors. On the other hand, high binding frequency means real chance of binding of the inhibitor is higher. Thus, compound-3 also could be a good inhibitor. Binding constant of compound-4 is higher than compound-1 and compound-2, but, less than compound-3. Its binding frequency is very less, only 10%. Thus, it may not be as effective as other three compounds. Still, it is also a candidate for the HIV-1 CA inhibitor. All four compounds have the binding constants in the micro molar range. Thus, we could promote these compounds for further studies.

The docked structures of four inhibitors reported here are presented in figure 1 (for compound 1), figure 3 (for compound 2), figure 4 (for compound 3) and figure 5 (for compound 4). Compound-1 fitted perfectly within the binding pocket of the viral protein and binds to both sides of the loop which is the most desirable. Contrary to this, all other three inhibitors bind to any one side of the loop. Thus, after the inhibitor binding, there is still a small chance of assemble activity of this protein. In this regard, we may conclude that

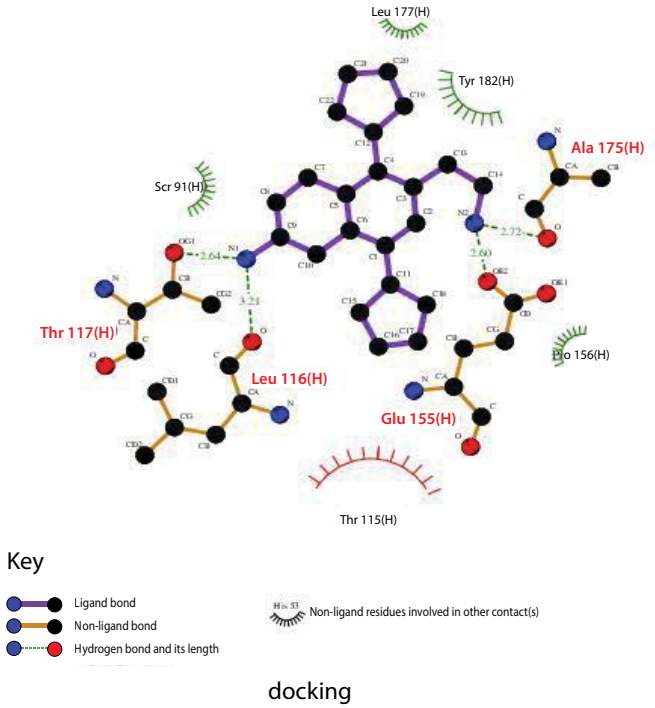

Figure 2: Interaction plot of compound-1.

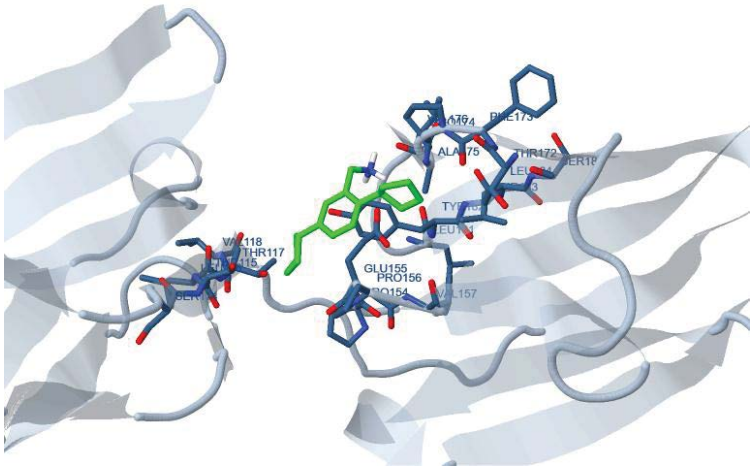

Figure 3: Docked structure of compound-2.

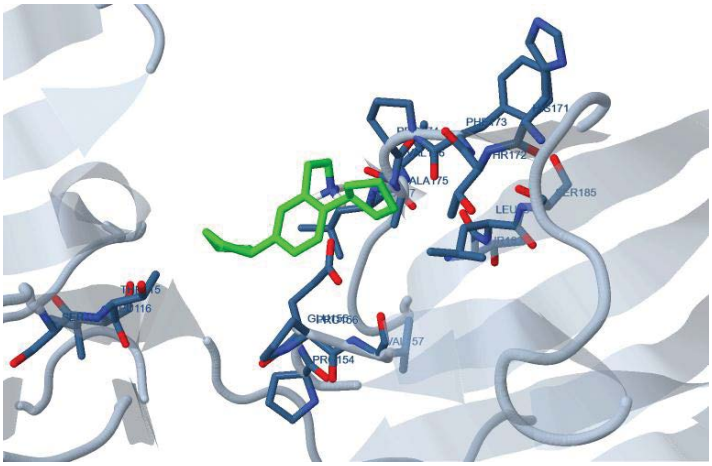

Figure 4: Docked structure of compound-3.

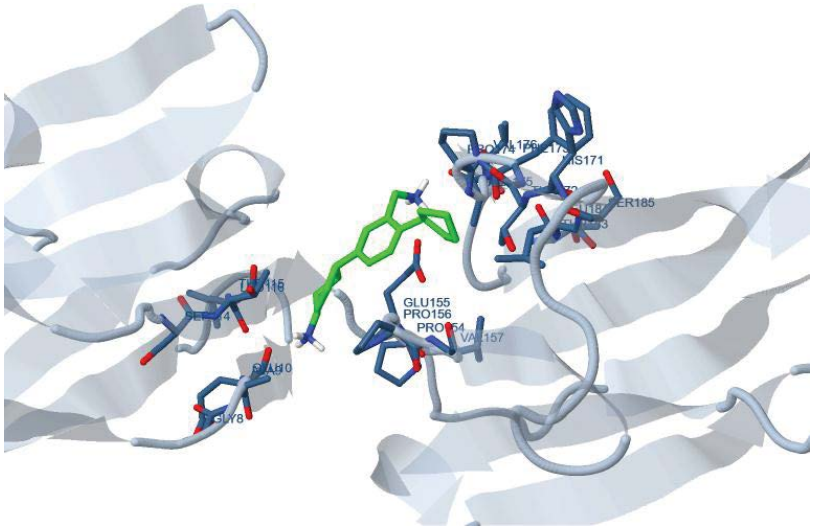

Figure 5: Docked structure of compound-4.

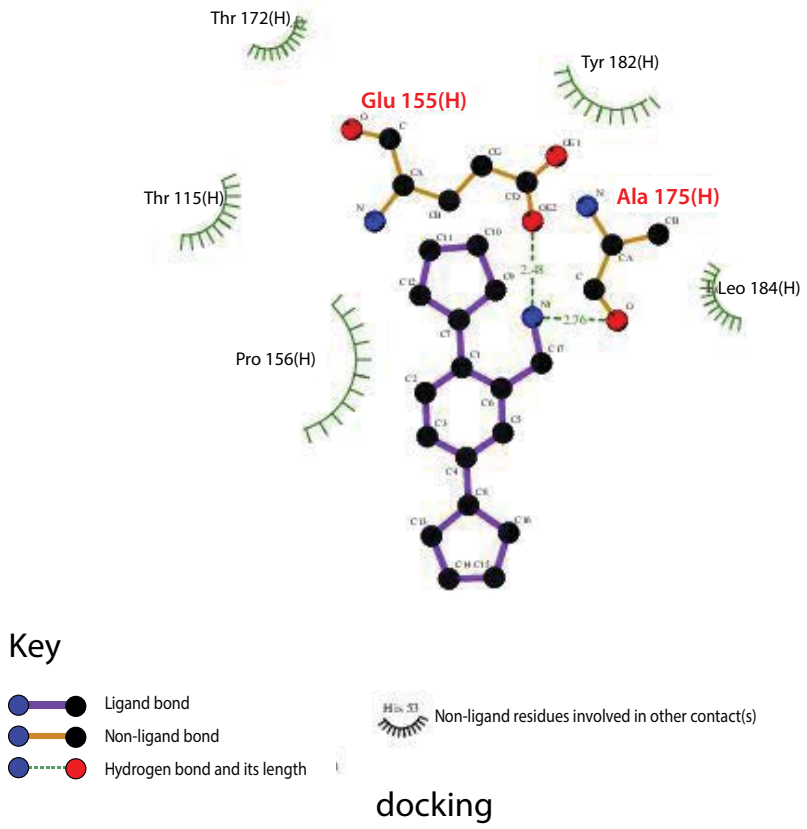

Figure-6: Interaction plot of compound-2.

compound-1 is the best inhibitor among these modelled compounds. There is another important observation. It is observed that in all cases, the key binding residues of CA protein are almost same. The binding residues and the nature of bindings are presented in figure 2 (for compound 1), figure 6 (for compound 2), figure 7 (for compound 3) and figure 8 (for compound 4). In these presentations, hydrogen bonding, vander Waals interactions and hydrophobic interactions are shown. From the interaction studies we found that all four compounds form hydrogen bonding with the 155 and 175 residues of CA protein which are Alanine and Glutamine, respectively. Additional interaction is observed for compound-1 which has interaction with Leucine and Threonine, two consecutive protein residues 116 and 117. It is also observed that all these compounds bind to the same binding site of the protein. Thus, their binding nature and effect would be the same.

Conclusion

From the present study we may conclude that four small organic compounds which are tested for HIV-1 CA inhibition activities are excellent findings for designing of HIV drugs

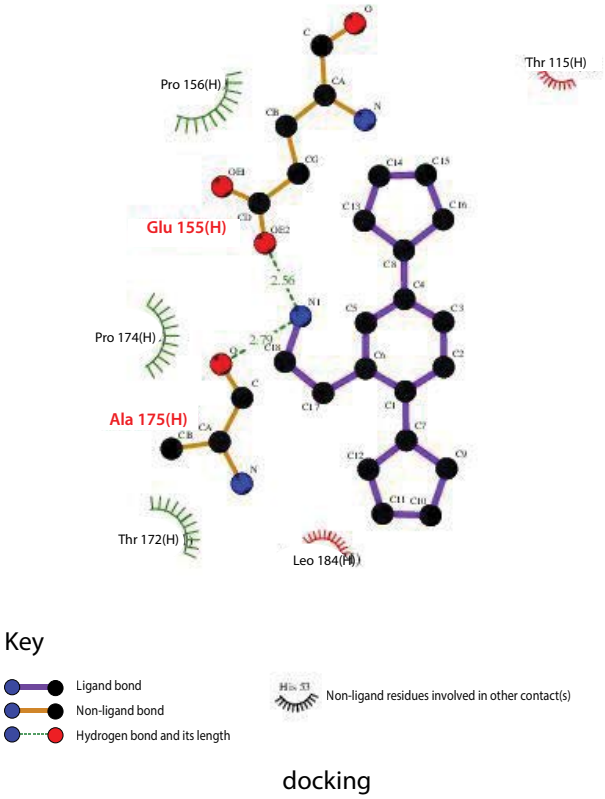

Figure 7: Interaction plot of compound-3.

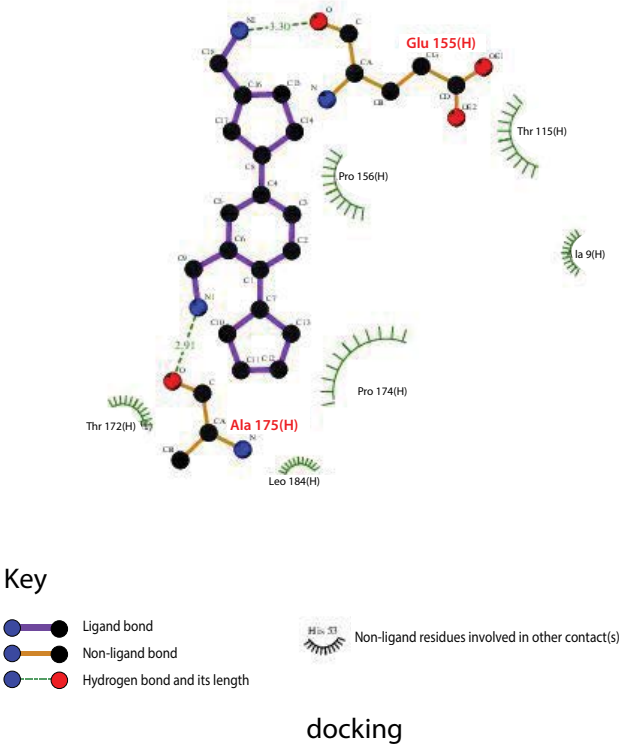

Figure 8: Interaction plot of compound-4.

as they have binding constant at the micro molar level and they are common organic compounds. Further experimental studies are required before pre-clinical tests. But, these compounds would definitely be cost effective drugs.

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