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Original Research Article

Molecular Docking of Pyrazole Inhibitors Against Integrase Receptor: A Computational Quantum Approach

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ABSTRACT

HIV/AIDS is an infection caused by a virus. Some drugs are known to be very potent in slowing the virus replication with good binding affinity with the receptor. However, there are some other drugs which have a significant and better docking approach with stronger binding affinity. Pyrazole derivatives are remarkably good and have been reported as better anti-HIV agents because they exhibit stronger binding affinity. In this study, a computational quantum approach was used to understand the binding interaction between the pyrazole derivatives and the receptor (Integrase). Docking is used to predict the bound conformation and binding free energy of small molecules to the target. The docking was carried out on ten pyrazole derivatives and their large negative binding affinity values in **kcal/mol** confirmed that they truly bind the pocket atoms of the receptor. The ligands have good negative binding affinity which showed that they are potent inhibitors for the receptor. The result obtained from the docking of the ligands with the receptor could be useful to design new potent anti-HIV-1 derivatives.

Keywords: Pyrazole Derivatives, Integrase, Binding affinity, Receptor, Ligand.

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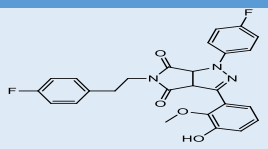
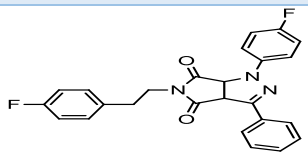
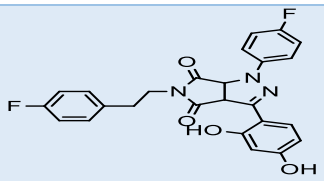
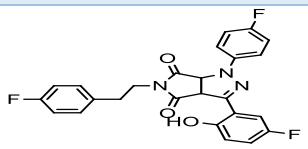
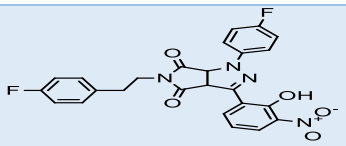
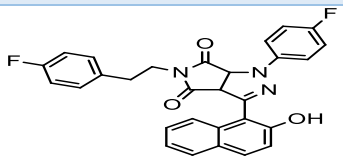
Introduction

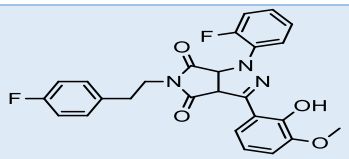
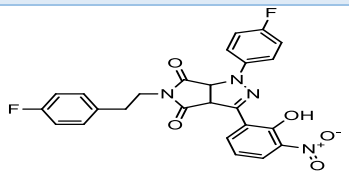
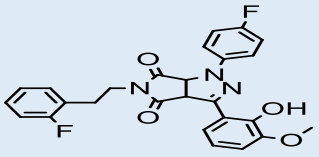
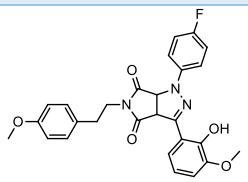
Human immunodeficiency virus type 1 (HIV-1) is the main causative agent of acquired immunodeficiency syndrome (AIDS), which remains a serious public health problem throughout the world [1]. The typical symptoms of HIV within a few weeks of infection include fever, sore throat and fatigue. Then the disease is usually asymptomatic until it progresses to AIDS. AIDS symptoms include weight loss, fever or night sweats, loss of appetite, dry cough, fatigue and recurrent infections. They four stages of HIV infection are: infection, Asymptomatic, symptomatic and progression of HIV to AIDS. Although HIV disease progression is described in stages, it is not inevitable that a person will go from stage 1 infection to stage 4 AIDS. There is treatment available that can prevent a person from developing AIDS and deal with the symptoms of HIV infection. The drugs which were screened and approved for the treatment of HIV can only dramatically slow down the disease's progress and also prevent secondary infections and complications [2]. The drugs are as follows: Nucleosides reverse transcriptase inhibitors (NRTIs), Non- nucleosides reverse transcriptase inhibitors (NNRTIs), Integrase inhibitors, Protease inhibitors [3]. HIV drugs development in the past was extremely slow due to the requirement of high level scientific expertise. Computational method is presently used and it is fast and less expensive. With the help of computational methods basic knowledge regarding the ligand and receptor can be acquired beforehand and also illustrate the interaction between the inhibitor ligand and the target site [4]. Molecular docking is widely used in virtual screening of millions of molecules to discover new lead compounds with biological activity [5]. Through molecular docking it is possible to study the 3D structure of the ligands in the protein pocket and analyze their possible conformations and orientations inside the protein. Molecular docking has been proved very efficient tool for novel drug discovery for targeting protein [6]. Protein-ligand docking refers for the search for the accurate ligand conformations within a targeted protein when the structure of proteins is known [7]. Our aim in this study is to carry out molecular docking in order to understand the binding mode and the binding interaction of the ten Pyrazole derivatives into the active site of Integrase receptor.

Materials and Method

The pyrazole derivatives used for this study were extracted from the literature [8]. The molecular docking study was carried out between Pyrazole derivatives and Integrase Receptor.

Table 1: Molecular structure of Pyrazole derivatives used in docking and their activities.

Ligand No	Structure	EC_{50} (μM)	$\log_{10}EC_{50}$
1		**5.37**	**5.2700**
2		**9.21**	**5.0357**
3		**35.31**	**4.4521**
4		**4.21**	**5.3757**
5		**7.55**	**5.1221**
6		**4.50**	**5.3468**

7		**112.85**	**3.9475**
8		**4.10**	**5.3872**
9		**2.52**	**5.5986**
10		**87.15**	**4.0597**

Preparation of Ligand

The structures of the inhibitors used in this docking were drawn using Chem draw and imported to Spartan 14 where their 3D structures were created. Their energies were minimized by molecular mechanics force fields (MMFF) to remove the strain energy before subjecting it to quantum chemical estimations. DFT (Density Functional Theory) with B3LYP (6-311G*) basis set was employed for complete optimization [9]. These structures were first saved in PDB format and imported to Pyrx software in order to make them ligands before docking using Auto Dock which converted the prepared file to PDBQT format. Auto Dock is a computational docking program based on empirical free energy force field and rapid Lamarckian genetic algorithm search method [10, 11].

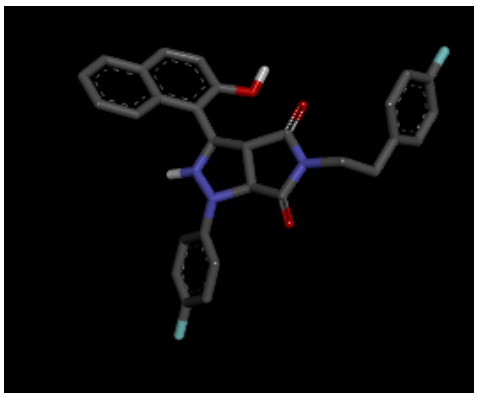


Figure 1: 3D structure of the prepared ligand 18.

Preparation of Receptor

The crystal structure of the receptor used in this study was obtained from protein data bank with PDB code **3OS1.** The water molecules and all other heteroatoms were removed from the protein crystal structure [12]. The prepared receptor was then saved in PDB file format which is the recommended input format in Pyrx and Discovery Studio Visualizer software [4]. The prepared structure was imported to Pyrx software for docking where it was first made macromolecule using AutoDock before docking it with the inhibitor.

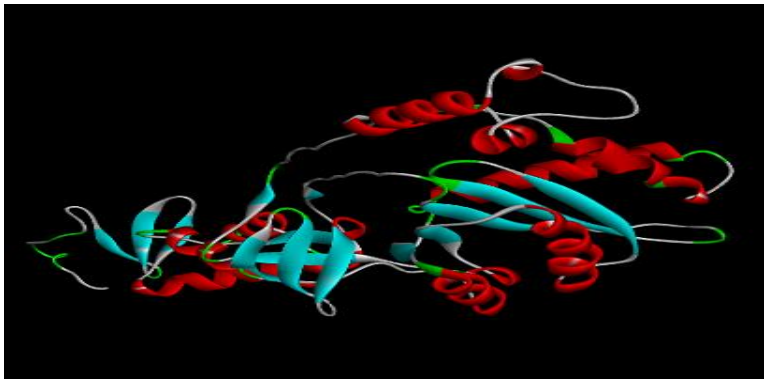


Figure 2: Prepared structure of the Receptor.

Ligand and Receptor Docking Process

The prepared ligand and receptor in figures 1 and 2 respectively above were docked using Pyrx software. Pyrx software is an open source with an intuitive user interface that runs all major operating systems. It is used to dock small molecule libraries to a macromolecule in order to find lead compounds with desired biological functions. Before the docking is initiated the vina

search space coordinates was reset in order to get the required coordinates of the ligand in the receptor pocket. After the docking process, the results were visualized, examined and evaluated using Discovery Studio software.

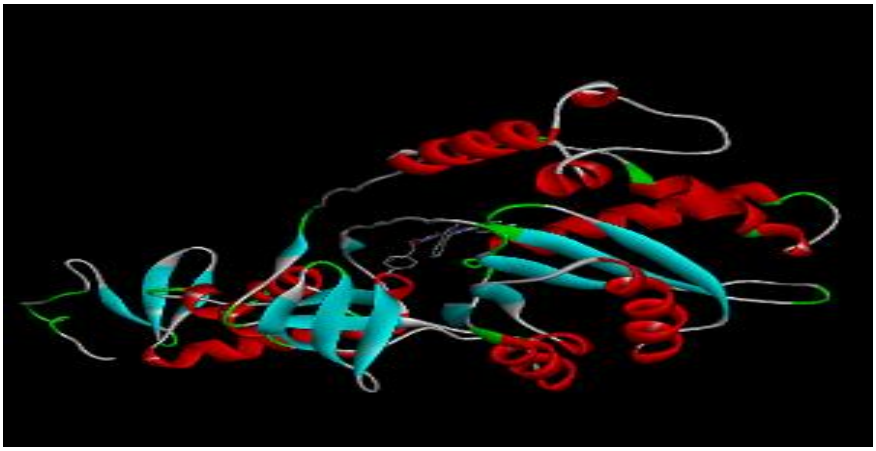
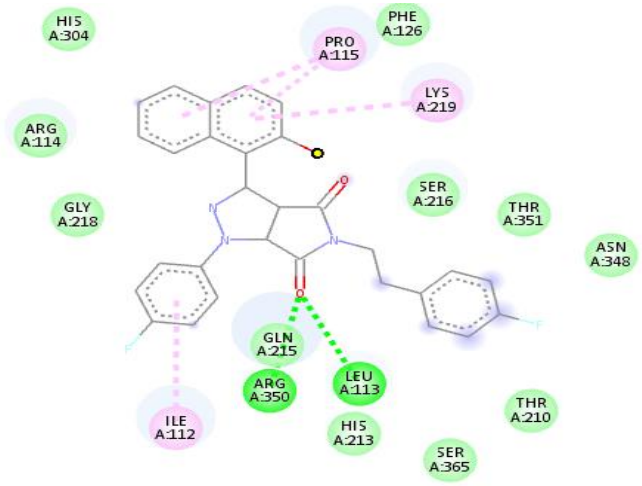


Figure 3: Receptor and ligand 6 after docking

Results



Interactions

Van der Waals

Pi-Alky

Conventional Hydrogen Bond

Figure 4: 2D interactions between Integrase receptor and Ligand 6.

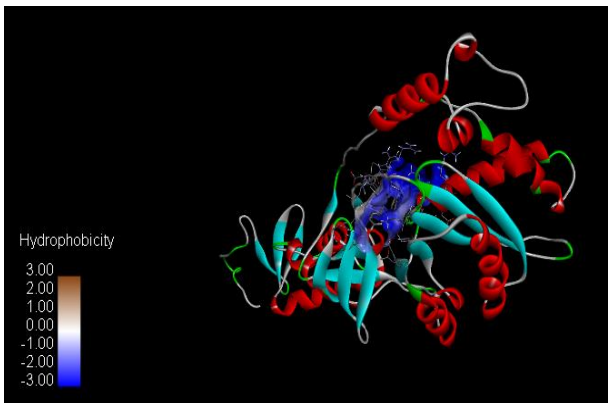


Figure 5: Hydrophobic interaction between ligand 6 and *Integrase receptor*

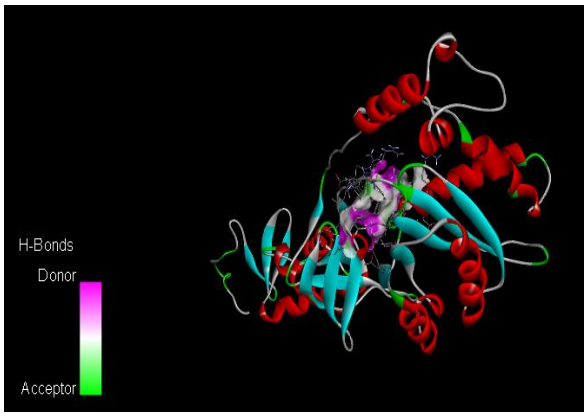


Figure 6: H-bond interaction between ligand 6 and *Integrase Receptor*

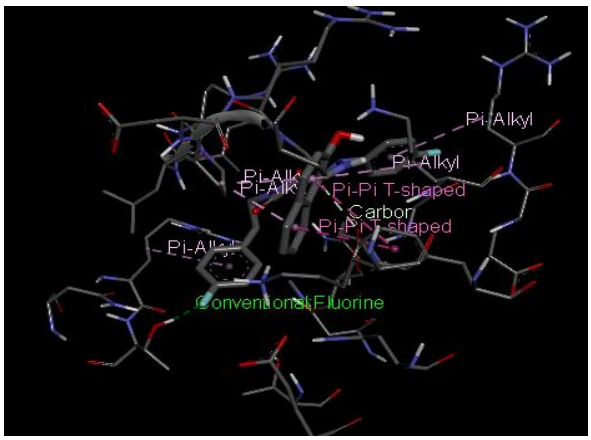


Figure 7: 3D interactions between Integrase Receptor and Ligand 6.

Table 2: Binding Affinity, Hydrogen bond interaction and hydrophobic interaction formed between the ligands and the active site of Integrase Receptor.

Ligand	Binding Affinity Kcal/mol	Hydrogen Bonding	Hydrophobicity		Dimension of Grid Center (X,Y,Z)
		Amino Acid	Amino Acid	Interaction	
1	-9.6	ARG 350	LYS 219, PRO 115, ILE 112	Pi-Alkyl	-47.089, 33.3301, -23.7978
2	-9.5	THR 351	PRO 115, ILE 112, ARG 350, LYS 219	Pi-Alkyl, Pi- Cation	-46.2133, 39.5018, -16.1825
3	-8.9	THR 351, GLN 215	ILE 112, PRO 115, LYS 219	Pi-Cation, Pi-Alkyl	-45.6975, 39.8411, -16.6526
4	-9.7	SER 216, LEU 113	HIS 213, ILE 112, PRO 115, ARG 350	Pi-Pi T-Shaped, Pi-Alkyl	-46.4894, 39.4867, -16.3838
5	-9.8	LYS 219	ILE 112, PRO 115	Pi-Alkyl	-46.9231, 38.3657, -15.7611
6	-10.3	LEU 113, ARG 350	PRO115, LYS219, ILE 112	Pi-Alkyl	-45.8504, 38.8083,-15.4986
7	-9.9	GLN 215, ARG 350	LYS 219, PRO 115, ILE 112	Pi-Alkyl	-46.7944, 37.8479, -16.659
8	-9.4	LYS 124, SER 216	LEU 113, LYS 219, ILE 112, PHE 126, PRO 115,ARG 350	Pi-Pi-T-Shaped, Amide-Pi Stacked, Pi-Sigma, Pi-Alkyl, Pi-Cation	-46.6908, 38.6679, -16.054
9	-9.2	_____	PRO 115, ILE 112, LYS 219,	Pi-Alkyl	-46.9579, 38.8758, -15.807

			LEU 113		
10	-9.3	THR 351, ARG 114	LYS 219, PRO 115, ILE 112, LEU 113, ARG 350	Pi-Cation, Pi-Sigma, Pi-Alkyl	-46.2027, 40.24, -16.0616

Discussion

Molecular docking studies were carried out in order to explain the interaction and the binding mode between the target Integrase Receptor and Pyrazole derivatives as potent anti-HIV agents. All the compounds were found to strongly inhibit by completely occupying the active sites in the target Receptor with their binding affinity values ranging from -8.9 to -10.3Kcal/mol. Among the ten inhibitors docked with the receptor, ligand 6 with the largest binding affinity of -10.3Kcal/mol as shown in Table 2 above was visualized and examined using discovery studio. Hydrogen bonds are generally considered to be facilitators of protein-ligand binding [13, 14]. The ligand formed two hydrogen bonds with LEU 113 and ARG 350 of the target site and forms hydrophobic bond with PRO115, LYS219 and ILE 112 of the target site. Hydrophobic interactions with non-polar residues PRO115, LYS219 and ILE 112 are suggested to increase the ligand binding affinity. Table 2 also reports that Ligand 18 with lower dimension of -45.8504, 38.8083, -15.4986 indicates that it is too close to bind the receptor pocket. Ligand 7 showed a better binding affinity of -9.9Kcal/mol with two hydrogen bonds with target site of Integrase. Generally, the hydrogen bond formation with the hydrophobic interaction provides evidence that the ligands are potent against Integrase receptor. Hydrogen donor and hydrogen acceptor region is shown in figure 6 above. Also, hydrophobic interaction between ligand 6 and Integrase receptor is shown in figure 5 above and the greatly affected the binding affinity.

Conclusion

Pyrazole derivatives were examined and evaluated for anti- HIV against Integrase receptor. High negative binding affinity was recorded and it correlates with their biological activities which indicated that they are excellent inhibitors for HIV integrase and the result obtained can be helpful to design new compounds with anti-HIV activity.

Acknowledgement

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