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Research Article

Probing the Frontier Molecular Orbitals, Electrostatic Potential Mapped onto the Electron Density Surface and the Binding Sites of Zidovudine (An Antiretroviral Drug) with HIV-1 Reverse Transcriptase

OV Ikpeazu[1], IE Otuokere[2]* and KK Igwe[3]

[1]*Department of Biochemistry, Abia State University, Uturu, Nigeria*

[2]*Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Nigeria*

[3]*Department of Vet Biochemistry and Pharmacology, Michael Okpara University of Agriculture, Umudike, Nigeria*

***Corresponding Author:** IE Otuokere, Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Nigeria.

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Abstract

Zidovudine (ZDV) is an antiretroviral drug used in the management of HIV/AIDS. Frontier molecular orbitals and electrostatic potential mapped onto the electron density surface were created using Arguslab software. Molecular docking studies of zidovudine with HIV-1 Reverse Transcriptase was performed using Patch dock and Fire dock online software servers. Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's (HOMO), lowest unoccupied molecular orbital's (LUMO) and electrostatic potential (ESP) mapped density. The Eigen values were calculated by geometry convergence function using PM3 method in ArgusLab software. The Eigen values for the HOMO and LUMO of zidovudine are -0.181960 and -0.014032 eV. The global binding energy predicted was -40.97 Kcal/mol. The hydrogen bonding sites are Gin 161(A), HOH 1096 (B), Asn 137 (B), Gly 93 (A), Try 181 (A), Met 184 (A) and Gin 182 (A). The steric interaction binding sites are Glu 138 (B), Asn 137 (B), Try 181 (A), Met 184 (A) and Gin 182 (A). These interactions were quite favorable due to negative free energy and suitable bond lengths.

Keywords: Zidovudine; HIV/AIDS; Arguslab Software; Molecular Docking; Orbitals

Introduction

Zidovudine (ZDV), conjointly called azidothymidine (AZT), is an antiretroviral drug used in the management of HIV/AIDS. It is usually suggested to be used with different antiretroviral. It can be used to stop mother to kid unfold throughout birth or once a needlestack injury occur. It is sold independently or in combination with lamivudine and abacavir. It can be administered orally or intravenously [1].

Zidovudine belongs to the class known as nucleoside reverse-transcriptase inhibitor (NRTI). It works by inhibiting the protein polymerase that HIV uses to create DNA and thus decreases replication of the virus [1]. It is normally employed in gestation and seems to be safe for the baby. It's side effects are headaches, fever, and nausea. Extensive side effects are liver issues, muscle harm, and high blood lactate levels.

Zidovudine was 1st delineated in 1964 [2]. In 1986, it was approved in the United States as the first treatment for HIV [3]. World Health Organization's Listed it as one of its Essential Medicines, the foremost effective and safe medicines required in a primary health system [4]. Zidovudine is sometimes treated double each day together with different antiretroviral therapies. This approach is observed as extremely Active Antiretroviral medical aid (HAART) and is employed to forestall the probability of HIV resistance [5,6]. Zidovudine has been used for post-exposure prevention (PEP) together with another antiretroviral drug referred to as nucleoside reverse transcriptase inhibitor (NRTI). Along they work to considerably cut back the danger of HIV infection following the primary single exposure to the virus [7]. Currently, zidovudine has been replaced by different antiretroviral like tenofovir to produce post-exposure prevention [8].

Currently, zidovudine is part of the clinical pathway for pre-exposure prevention and post-exposure treatment of mother-to-child transmission of HIV throughout gestation, labour, and delivery and has been tested to be integral to clean siblings' perinatal and infant development [9]. Without NRTI, ten to fifteen percent of fetuses with HIV-infected mothers can themselves become infected [10]. NRTI has been shown to scale back this risk to as very little as 8 percent once it is administered before conception, during delivery and after delivery [11]. NRTI was the first kind of hindrance

of mother-to-child HIV transmission in 1994 to 1999. NRTI prevention prevented over a thousand parental and baby deaths from AIDS in the United States [12].

Even at the best doses which will be tolerated in patients, NRTI is not potent enough to forestall all HIV replication. It only slows the replication of the virus and progression of the malady. Prolonged NRTI treatment will result in HIV developing resistance to NRTI by mutation of its polymerase [13,14]. To slow the event of resistance, physicians usually advocate that zidovudine be used together with other polymerase inhibitor and an antiretroviral from another cluster, like an antiviral agent, non-nucleoside polymerase substance, or integrase inhibitor; this kind of medical aid is known as highly active antiretroviral therapy.

Zidovudine is an analogue of thymidine. NRTI works by selectively inhibiting the enzyme that the virus uses to create a DNA copy of its RNA. This enzyme is known as HIV's reverse transcriptase. Reverse transcription is critical for production of HIV's double-stranded DNA, which might be afterward integrated into the genetic material of the infected cell [15-17].

Materials and Methods

The structure of zidovudine was drawn and constructed using window based program of Arguslab and ACDl ab Che Sketch software's. Conformational analysis (geometry optimization) of zidovudine was carried out using PM3 semi-empirical QM parameterization method by ArgusLab 4.0.1 software. Geometry of the molecule was converged after the molecule was drawn and cleaned in Arguslab and the program computed the energy until the maximum cycles reached for the convergence (stopping point) of the molecule. Surfaces were created to visualize the excited state properties such as Highest Occupied Molecular orbital (HOMO), Lowest Unoccupied Molecular Orbitals (LUMO), electrostatic potentials (ESP) mapped density surface.

Molecular docking

Docking studies were performed using the Patch dock and firedock online software packages. The protein data bank (PDB) files of the crystal structures of HIV-1 Reverse transcriptase having PDB entry number 1REV was downloaded from the protein data bank website. Regularization and optimization for protein and ligand were performed. Determination of the essential amino acids in binding site were carried out and compared with the present literature. The interactive docking method was carried out for all the conformers of each compound in the selected active site. The docked compound was assigned a score according to its fit in the ligand binding pocket (LBP) and its binding mode.

Results and Discussion

Figures 1 and 2 shows the Highest Occupied Molecular Orbital of molecule (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) of zidovudine respectively. Figure 3 shows electrostatic potential mapped onto the electron density surface of zidovudine. The molecular docking and ligand map of zidovudine are shown in Figures 4 and 5 respectively.

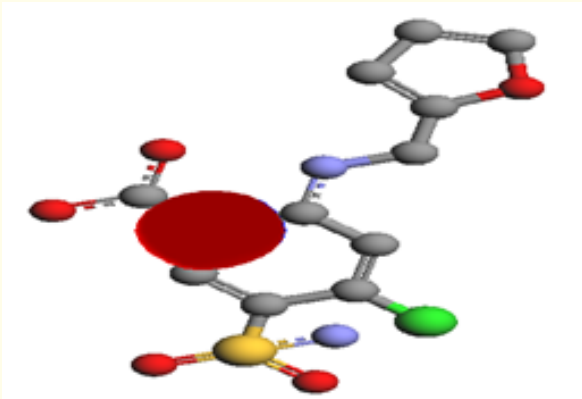

Figure 1: Highest Occupied Molecular Orbital of Molecule (HOMO) of Zidovudine.

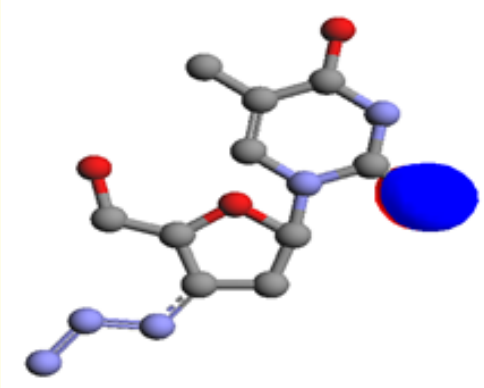

Figure 2: Lowest Unoccupied Molecular Orbital (LUMO) of Zidovudine.

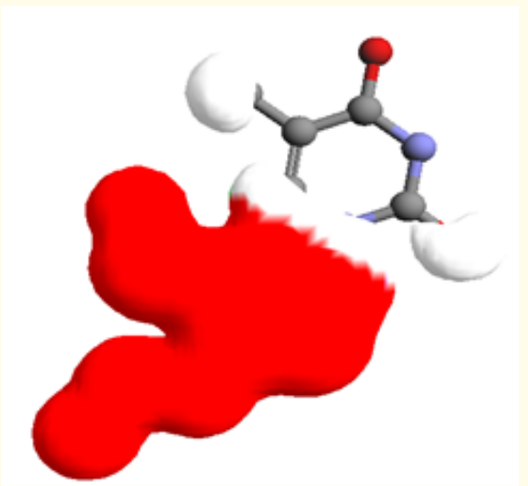

Figure 3: Electrostatic Potential Mapped onto the Electron Density Surface of Zidovudine.

Figure 4: Zidovudine Docked with HIV-1 Reverse Transcriptase.

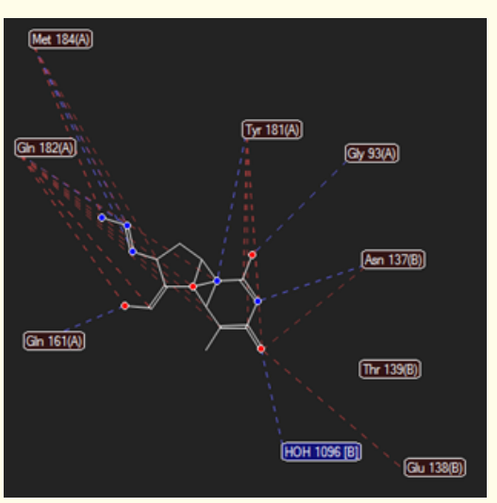

Figure 5: Zidovudine Ligand Map Showing its Interactions with Amino Acid Residue in HIV-1 Reverse Transcriptase.

The HOMO of zidovudine (Figure 1) is the orbital of highest energy that is still occupied, therefore energetically it's the best to get rid of electrons from this orbital. This might be merely donating negatron density to make a bond. The LUMO of zidovudine (Figure 2) is the lowest lying orbital that is empty, therefore energetically it's the best to feature a lot of electrons into this orbital. The Eigen values for the HOMO and LUMO of zidovudine, molecular orbital number 45 and 46 are -0.181960 and -0.014032 (Table 1).

Molecular Orbital number	45 (HOMO)	46 (LUMO)
Eigen values	-0.181960	-0.014032

Table 1: Energy Values of the Frontier Molecular Orbitals of Zidovudine.

ArgusLab was used in generating Electrostatic potential mapped onto the electron density surface of zidovudine (Figure 3). Electrostatic potential maps are three dimensional diagrams of molecules. It permits us to check the charge distributions of molecules and charge connected properties of molecules.

They conjointly enable us to check the dimensions and form of molecules. In chemical science, static potential maps are valuable in predicting the behaviour of advanced molecules. Molecular electrostatic potential maps conjointly illustrate information concerning the charge distribution of a molecule, the properties of the nucleus and nature of electrostatic energy. For simplicity, think about moving a charge on the spherical isosurface of atom. The charged nucleus emits a radially constant field of force. The area higher than average electrostatic potential energy indicates the presence of a stronger electric charge or a weaker negative charge. Given the consistency of the nucleus electric charge, the upper potential energy worth indicates the absence of negative charges, which might mean that there are fewer electrons during this region. Therefore, a high electrostatic potential indicates the relative absence of electrons while low electrostatic potential indicates an abundance of electrons. To accurately analyse the charge distribution of a molecule, a really great quantity of electrostatic potential energy values should be calculated. The most effective way to convey this knowledge is to visually represent it, as electrostatic potential map. The red region of the surface is the lowest electrostatic potential energy while the blue region is the highest.

Electrostatic potential surfaces are valuable in computer-aided drug design because they assist in understanding electrostatic interactions between the macromolecule and the drug. These surfaces can be used to compare different inhibitors with substrates. Electrostatic potential surfaces will be either displayed as isocontour surfaces or mapped onto the molecular negatron density. The shape of a molecule is decided by the negatron density of the molecule.

The docking score has been ranked according to their global energy (Table 2). The global energy is the binding energy of the solution. The contribution of the van der Waals forces and atomic contact energy (ACE) to the global binding energy have been shown (Table 2). The best binding energy (minimum energy) is -40.97 Kcal/mol. The negative value of the binding energy shows

that the zidovudine can selectively inhibit the enzyme that the virus uses to create a DNA copy of its RNA. This enzyme is known as HIV's reverse transcriptase.

Rank	Solution Number	Global Energy	Attractive VdW	Repulsive VdW	ACE
		↓			
1	1	-40.97	-16.48	2.28	-11.63
2	2	-38.24	-15.55	1.56	-11.11
3	8	-36.53	-14.61	2.22	-10.30
4	5	-35.33	-15.17	4.24	-10.37
5	10	-34.58	-13.71	3.35	-10.62
6	6	-33.61	-14.49	2.95	-9.25
7	3	-32.15	-13.54	2.59	-8.99
8	4	-31.30	-13.38	4.85	-9.71
9	9	-26.18	-13.13	1.86	-5.06
10	7	-25.57	-13.30	1.06	-4.39

Table 2: Docking Score of Zidovudine in Complex with HIV-1 Reverse Transcriptase.

Hydrogen bonding and steric interactions were observed in zidovudine ligand map (Figure 5). Hydrogen bonding occurred with Gin 161(A), HOH 1096 (B), Asn 137 (B), Gly 93(A), Try 181(A), Met 184 (A) and Gin 182(A) with bond length 3.08, 0.00, 3.19, 3.45, 3.06, 2.43 and 3.26 Å respectively. The strength of the bonds is -2.50, -0.46, -1.30, -0.75, -2.50, -1.05 and -1.31 Kcal/mol respectively. These interactions were quite favorable due to negative free energy and suitable bond lengths. Steric ininteractions occurred with Glu 138(B), Asn 137(B), Try 181(A), Met 184(A) and Gin 182 (A).

Conclusion

The negative values of the global energy and atomic contact energy (ACE) showed that the interactions were quite favourable. The interactions are hydrogen bonding and steric interactions.

Acknowledgements

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Conflict of Interest

No conflict of interest.

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