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Electronic Structure and Molecular Docking Studies of an anti-HIV Drug: Stavudine

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For anti HIV activity, Stavudine (or D4T or Zerit) is an important nucleoside reverse transcriptase inhibitor (NRTI). Molecular geometry of this compound has been optimized by DFT B3LYP/6–31G (d,p) method using Gaussian 03 software package. In order to examine global reactivity descriptors of the drug molecule, Frontier orbital analysis has been carried out. Using molecular docking inhibition activity of the drug against HIV-1 reverse transcriptase (6AN2) has been investigated. Attempts have been made to elucidate the chemical and biological properties of the drug.

Keywords: Drug, HIV, DFT, Molecular docking.

Introduction

The anti-HIV, 2′, 3′-didehydro-3′-deoxythymidine (stavudine or D4T or Zerit) belongs to the family of nucleoside reverse transcriptase inhibitors (NRTIs). Stavudine prevents HIV from altering the genetic material of healthy CD4 cells.[1] It hinders living cells from producing new virus and decreases the amount of virus in the body. The present paper reports the structure, conformation, potential energy surface and simulation of this antiviral drug using quantum chemical methods. A plenty of literature dealing with the structural and/or conformational transitions in the drug molecule and its role in altering pharmacological effectiveness is presently available in literature.[2,3]

Computational methods

Molecular simulation and modelling are undergoing rapid development. They are increasingly important tools for fundamental and applied research in academia and industry in such diverse fields as drug-design and materials science.[4–7] In the present investigation, the drug molecule and nucleic acid bases are optimized by B3LYP method[8] with 6–31G (d,p) basis set using Gaussian 03 program.[9] For molecular docking studies, SwissDock web server has been used.[10]

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Results and discussion

Equilibrium geometry

The molecular geometry of stavudine has been optimized by DFT (B3LYP) method with 6–31G (d,p) basis set using Gaussian 03 program. The optimized molecular geometry along with various atomic index numbers and bond lengths of drug molecule has been shown in Fig. 1.

Frontier orbital analysis

The HOMO and LUMO of stavudine are shown in Fig. 2. The electronic parameters of the drug are listed in Table 1. The calculated electronic parameters include ionization potential, electron affinity, absolute electronegativity and chemical hardness etc. These parameters are used to describe chemical reactivity of molecules.

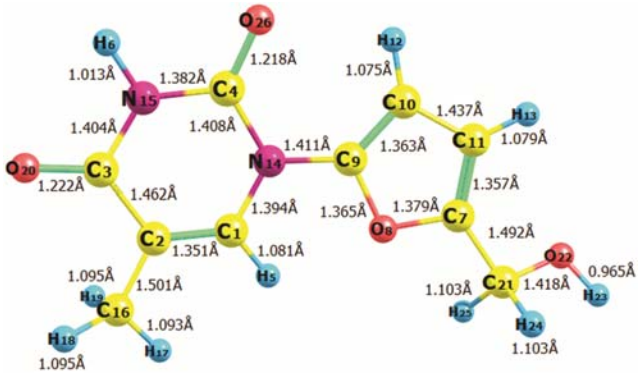

Fig. 1 — Equilibrium molecular geometry of stavudine drug

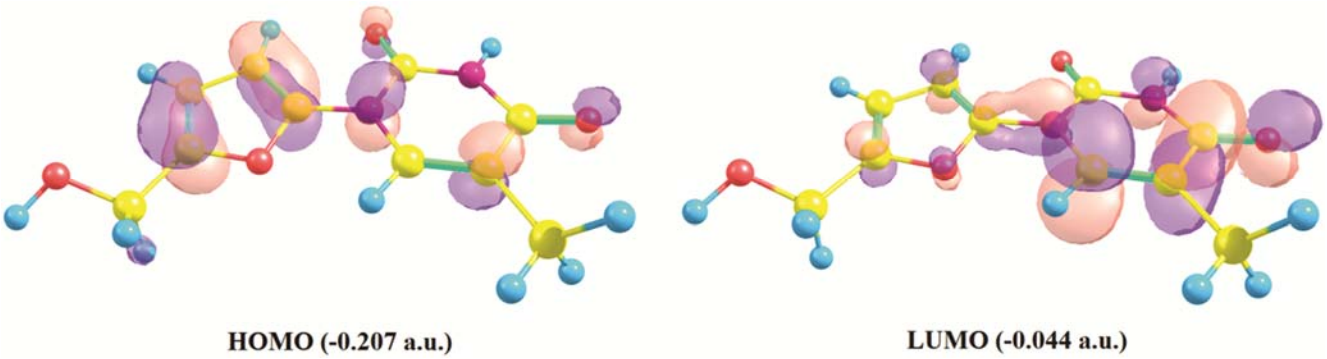

Fig. 2 — HOMO and LUMO of stavudine

Table 1 — Electronic parameters of stavudine as calculated by B3LYP/6-31G(d,p) method

Electronic Parameter	
HOMO energy	-0.207 a.u.
LUMO energy	-0.044 a.u.
Energy Gap (ΔE)	0.163 a.u.
Ionization Potential (I)	0.207 a.u.
Electron Affinity (A)	0.044 a.u.
Electronegativity (χ)	0.125 a.u.
Electronic chemical potential (μ)	-0.125 a.u.
Global hardness (η)	0.081 a.u.
Global softness (S)	12.34 $a.u.^{-1}$
Electrophilicity index (ω)	0.096 a.u.

Molecular docking

Molecular docking is a process that explores the binding of a drug molecule with a receptor and thereby estimates the effectiveness of drug. Thus docking has a great importance in the field of drug discovery.[4, 5] In this process all possible conformers of the molecule (ligand) and their corresponding energy values are calculated and finally the best binding modes are ranked according to the full fitness (FF) score. In order to avoid sampling bias the whole docking process performed by SwissDock is blinded by covering the entire protein and not defining any specific region of the protein as bonding pocket. The resulting output clusters obtained after each run showed that cluster 0 is having the best full fitness (FF) score. The title compound shows anti HIV-1 activity, so we have performed the docking study of the drug with HIV-1 reverse transcriptase (PDB ID: 6AN2).[11] The FF score and binding affinity obtained for protein targets clearly show that the drug molecule effectively bonded with 6AN2 target by forming two hydrogen bonds of 2.099Å and 2.432Å (FF score:-3512.208 kcal/mol, binding affinity ΔG = -7.535 kcal/mol). The docking picture obtained from the UCSF chimera software is shown in Fig. 3. From this result, we can say that this compound effectively acts as an anti-HIV type-1 drug.

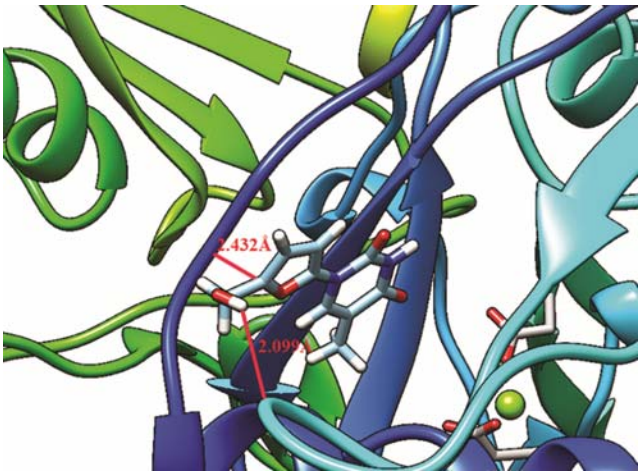

Fig. 3 — Molecular docking of stavudine with 6AN2 receptor

Conclusion

Chemical reactivity and charge transfer within the drug stavudine molecule has been elucidated by Frontier orbital surface analysis. Molecular docking suggested that drug elicits its potential antiviral activity against HIV by forming strong hydrogen bonding with 6AN2 receptor.

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References

1 Palafox M A & Iza N, Structure of the antiviral stavudine using quantum chemical methods: Complete conformational space analysis, 3D potential energy surfaces and solid state simulations, *J Molec Struct*, **1028** (2012) 181–195.

2 Brennan A T, Davies M A, Bor J, Wandeler G, Stinson K, Wood R, Prozesky K, Tanser F, Fatti G, Boulle A, Sikazwe I, Wool-Kaloustian K, Yuannoutsos C, Leroy V, de Rekeneire N, Fox M P, Has the phasing out of stavudine in accordance with changes in WHO guidelines led to a decrease in single-drug substitutions in first-line antiretroviral therapy for HIV in sub-Saharan Africa?, *AIDS*, **31** (2017) 147–157.

3 Yadav E, Singh M & Saxena P N, Structure activity relationship of some type II pyrethroids: A study based on atomic charges, molecular electrostatic potential surfaces and molecular orbitals analysis, *Nat Acad Sci Lett*, **37** (2014) 245–251.

4 Tiwari G, Srivastava A K, Kumar R & Kumar A, Quantum chemical and molecular docking studies on two potential hepatitis C virus inhibitors, *Main Group Chem*, **18** (2019) 107–121.

5 Bapat S, Viswanadh N, Mujahid M, Shirazi A N, Tiwari R K, Parang K, Karthikeyan M, Muthukrishnan M & Vyas R, Synthesis, biological evaluation and molecular modeling studies of Novel Chromone/ Aza-Chromone fused α-aminophosphonates as Src Kinase inhibitor, *J Sci Ind Res*, **78** (2019) 111–117.

6 Monga D, Soni S & Satsangi P S, Role of optical properties on photon distribution in a biological tissue using Monte Carlo method, *J Sci Ind Res*, **76** (2017) 154–159.

7 Ramesh K V, Solanki M, Sharma S & Deshmukh S. Molecular dynamics simulation of homology modeled 2-nitropropane dioxygenase from Mycobacterium tuberculosis, *J Sci Ind Res,* **74** (2015) 277–280.

8 Mardirossian N & Head-Gordon M. Thirty years of density functional theory in computational chemistry: an overview and extensive assessment of 200 density functional, *Mol Phys*, **115** (2017) 2315–2372.

9 Frisch M J et al. Gaussian Inc., Wallingford CT Gaussian 03, Revision C.02 (2004).

10 Grosdidier A, Zoete V & Michielin O, SwissDock, a protein-small molecule docking web service based on EADock DSS, Nucleic Acids Research **39** (2011) W270–W277.

11 https://www.rcsb.org/structure/6AN2