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DFT and Molecular Docking Studies of an Antiviral Drug: Molnupiravir

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This paper presents computational analysis of molnupiravir, the first orally administered antiviral drug approved by MHRA for the cure of COVID-19. Molnupiravir is the derivative of N4-hydroxycytidine with a ribose residue attached to an isobutyrate ester group. Method based on DFT has been employed to establish the optimised structure, electronic and optical parameters of the drug molecule. Further, molecular docking of molnupiravir on SARS-CoV-2 protein, glucocorticoid receptor (PDB ID: 1M2Z) has been performed so as to examine the preferred affinity and binding pattern of the drug.

Keywords: Molnupiravir; COVID-19; Glucocorticoid receptor; DFT

1 Introduction

COVID-19 is the infectious respiratory disease caused due to SARS-CoV-2 virus, which firstly emerged in Wuhan, China in December 2019[1]. The triggered pandemic invoked globally significant impact on health issues, economy, and social systems[2].

For the treatment of COVID-19, an antiviral drug molnupiravir, originally developed by Emory University and Ridgeback Biotherapeutics is now being manufactured by Merck & Company, under the brand name of Lagevrio[3]. The drug works by introducing errors into the genetic material of the virus, which then prevents the virus from replicating and spreading. This drug is taken orally and is designed to be effective against a broad range of RNA viruses, including SARS-CoV-2[4].

In view of these facts, the present in silico investigation of the physico-chemical and molecular docking properties of the molnupiravir drug has been undertaken. To accomplish the goal, the widely used Density Functional Theory (DFT) method has been utilised. To determine the relative reactivity of the drug, global reactivity descriptors have been obtained using the energy of HOMO and LUMO orbitals. Additionally, we have used molecular docking technique to examine the binding sites of the drug with protein receptor of SARS-CoV-2[5-7].

2 Theoretical Methods

The study has employed Gaussian 16 program package and GaussView 6.0 to fully optimize the ground state geometry of molnupiravir without any symmetry restrictions[8-9]. DFT method associated with B3LYP hybrid functional blended by 6-311 G (d, p) basis set has been used for calculations. Molecular docking simulation of the drug with the SARS-CoV-2 protein has been performed using SwissDock. Finally, docked complexes are visualised by Chimera software[10-11].

3 Results and Discussion

The optimized geometry along with various bond lengths of molnupiravir drug is exhibited in Fig. 1

The calculated electronic parameters and global reactivity descriptors of molnupiravir drug are listed in Table 1.

3.1 MEP Surface and Frontier Orbitals Analysis

The MEP surface of molnupiravir is depicted in Fig. 2. In it colour shades signify the negative, positive and neutral potential zones. Nitrogen atom creates the most electronegative region and hence a favourable site of electrophilic attack.

Electron donating and electron accepting abilities of a molecule are characterized by its HOMO and LUMO energy and chemical reactivity is estimated by the difference between them. In case of molnupiravir drug, LUMO-HOMO energy gap comes out to be 5.038 eV; which makes it chemically moderately stable. The HOMO- LUMO surfaces of the molnupiravir drug are depicted in Fig. 3. The global chemical reactivity descriptor parameters obtained using HOMO and LUMO energies, are mentioned in Table 1. Here chemical reactivity depends on the structural arrangement of the

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Table 1 — Electronic and global reactivity descriptor parameters of molnupiravir drug

Total energy	-32597.826 eV
Dipole moment	4.547 Debye
HOMO energy	-6.848 eV
LUMO energy	-1.810 eV
Frontier orbital energy gap	5.038 eV
Chemical potential (μ)	-4.329 eV
Electronegativity (χ)	4.329 eV
Electron affinity (EA)	1.810 eV
Ionization potential (I)	6.848 eV
Global hardness (η)	2.519 eV
Global softness (S)	0.397 eV^{-1}
Global electrophilicity (ω)	13.702 eV
Maximum additional electric charge (ΔN max)	1.719

molecule. The formulae related to global reactivity descriptors may be found in the literature[5-7].

The ionization potential of molnupiravir is 6.848 eV, which makes it a good donor. When addition of an electron to a neutral molecule is done, the released energy is known as electron affinity. Table 1 evidences that molnupiravir drug is moderately reactive (EA= 1.810 eV). The extent of the stabilization of the system is obtained by electrophilicity index (ω) when electrons come from the environment to saturate the system (atom/molecule). A nucleophile, more reactive, good system is symbolised by a lower value of ω and vice versa. For molnupiravir, electrophilicity index (ω = 13.702 eV) is selectively lower and therefore it is a good nucleophile.

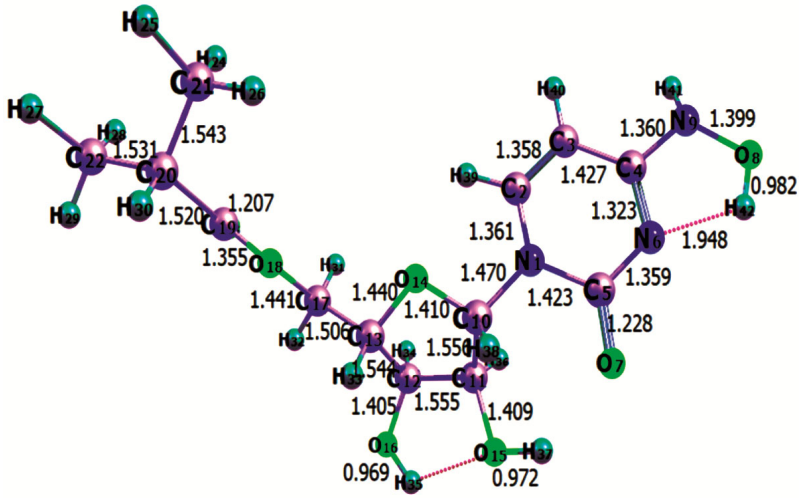

Fig. 1 — Optimized structure of molnupiravir drug.

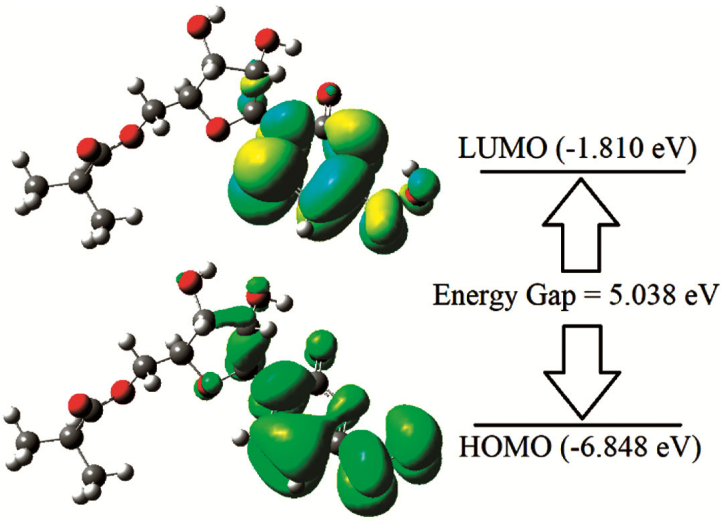

Fig. 2 — Frontier orbitals of molnupiravir drug.

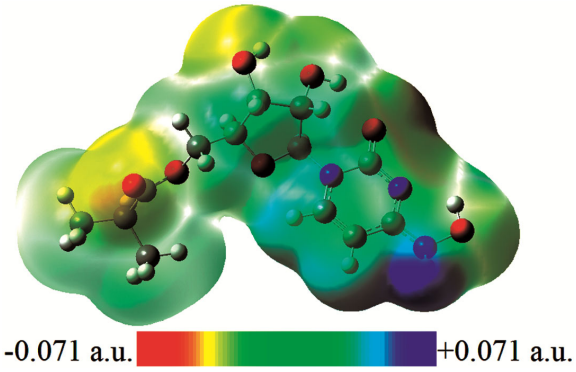

Fig. 3 — MEP surface of molnupiravir drug.

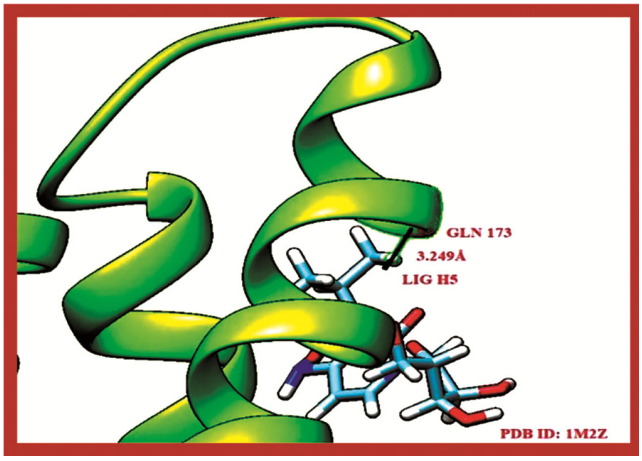

Fig. 4 — Molecular docking of molnupiravir drug.

3.2 Molecular Docking

In drug design, molecular docking is frequently used as it helps to simulate the interaction of the ligand (drug/molecule) with receptor (protein) and predict their binding preference. Binding modalities are arranged as per full fitness score. To avoid sampling bias, docking simulation has been accomplished by using blind folded Swiss Dock web server. Herein the entire protein receptor is enveloped instead of considering its particular zone as the binding location. Evidently several molecular associations of receptor with molnupiravir are observed (Fig. 4). However, association between the residue GLN (173) and molnupiravir LIG (H5) having energy of -6.12 kcal/mol, separated by 3.249 Å with FF score of -2772.41 kcal/mol appears to be most stable one. Thus docking results suggest that molnupiravir drug elicits more binding preference for the LIG (H5) with the residue GLN (173) of 1M2Z protein receptor[5,12,13].

5. Conclusion

Based upon the results of electronic properties, global reactivity descriptors, MEP surface and HOMO-LUMO analysis and molecular docking simulation discussed in the paper, it may be concluded that molnupiravir drug carries potential to effectively inhibit SARS-CoV-2.

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