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DFT STUDY OF THE COCRYSTAL BETWEEN FAVIPIRAVIR AND LAMIVUDINE

Abstract: *The DFT method was used to analyze some quantum-chemical parameters of known drugs - Favipiravir and Lavimidine and their co-crystals. And also an analysis of the surface of the electrostatic potential of the co-crystal and its main components was carried out. Furthemore, non-covalent interactions of cocrystal is visualized using MultiWFN and VMD program packages.*

Key words: *Favipiravir, Lavumidine, DFT, QSP, NCI, HOMO, LUMO.*

Language: *English*

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Introduction

It is known that in recent years, computational methods based on density functional theory (DFT) have been widely used to solving chemical problems [1-3]. DFT calculations by modern basis sets can be performed on several computational programs (GAMESS [4], Firefly [5], Gaussian [6], ORCA [7], etc.). In one side, It is possible to directly determine the spatial structure of the compound, the charge distribution on atoms (q_A), the energies of molecular orbitals and the fraction of atoms in them, spectra, dipole moment and other theoretical parameters from the calculation results. In other side, indirectly can be determined the Hirshfeld index, analysis of electrostatic potential levels (ESP), density of states (DOS - density of states), localization and delocalization indices of the molecule, LOL (localized orbital localizer), NCI (non-covalent interactions) [8-9]. Non-covalent interactions (VdV interactions, hydrogen bonds, phase effects, etc.) are of great

importance in chemistry. These interactions play an important role in the formation of single-crystals of compounds and in crystal packing in crystal cells. Therefore, the most useful quantum-chemical parameters (QSP) of favipiravir, lamivudine and their cocrystal were studied by the DFT method.

The objects of our study are cocrystal of Favipiravir and Lamivudine. Favipiravir (Avigan) is a new antiviral medication developed by Fuji Film Company and Toyama Chemical with effectiveness against viral infectious diseases such as Ebola virus [10,11]. Several laboratory studies have shown the effectiveness of favipiravir against Ebola virus. Lamivudine (3TC) is an antiretroviral medication that reduces the amount of HIV in the body. Anti-HIV drugs such as lamivudine slow down or prevent damage to the immune system, and reduce the risk of developing AIDS-related illnesses. Lamivudine is also active against hepatitis B virus (HBV). The latest news and research on HIV treatment Lamivudine is available as part of several co-formulations [12].

Materials and methods.

The geometry of the cocrystal (Fig.) was obtained from the single crystal XRD data (cif file), which will be printed anywhere, and it has been fully optimized by the DFT/def2-TZVP method using ORCA 4.2.0 program package [13]. The Hybrid method of Becke [14] with three parameters and correlation functions of Lee, Yang and Parr [15] was chosen as a DFT (B3LYP) method. The def2-TZVP method is developed by Ahlirichs group [16] and it successfully used in our previous works [17].

The geometries of favipiravir's tautomeric forms and lamivudine were built using the ORCA modified Avogadro [18] program package. And also, Avogadro program have been used for visualizing frontier electron densities and atomic charges by Malliken.

The surface analysis of electrostatic potential (ESP) and non-covalent interactions (NCI) have been carried out using MultiWFN [19] and VMD [20] program packages.

Results and discussion.

Due to the high biological activity of favipiravir and lavumidine, the compounds were confirmed for experimental and theoretical studies [10-12]. Antonov [21] has investigated the tautomerism of Favipiravir by DFT method and determined relative stability of the enol form. The keto form of Favipiravir is obtained in cocrystal of Favipiravir with Lavumidine. Therefore, we calculated QSP for both tautomeric forms of favipiravire, Lavumidine and their cocrystal (Fig.1).

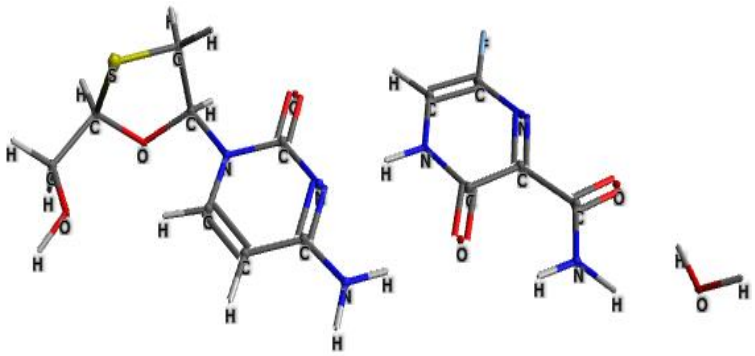

Fig.1. Optimized cocrystal of Favipiravir with Lavumidine and one molecule of water.

Charge distribution on atoms is one of the important quantum chemical parameters in chemistry, which shows the relative charge density in the vicinity of an atom.

The largest negative charge is located in oxygen atom of keto (q_O=-0.41) and enol (q_O=-0.43) group in the case of Favipiravir (Fig.2). The largest negative charge is located in oxygen atom of OH group, in the case Lavumidine. A significant change in negative charges on the above indicated oxygen atoms are found in the cocrystal.

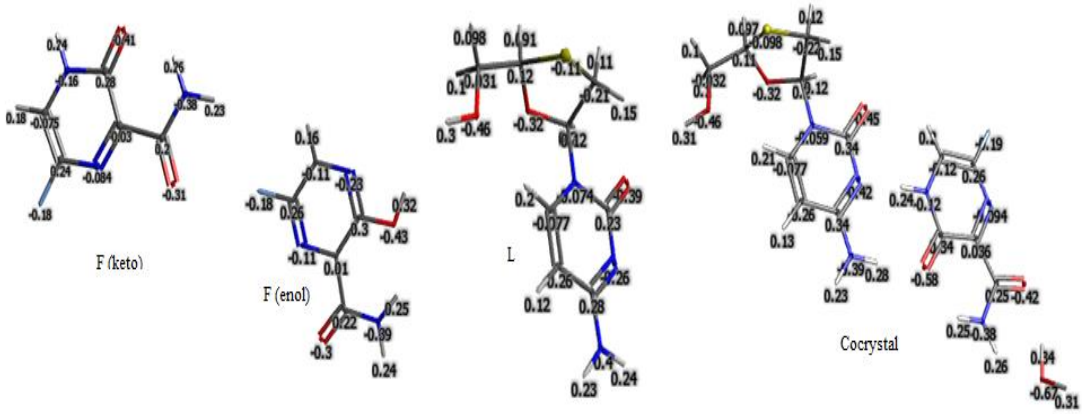

Fig.2. Charge distribution on the atoms of the studied compounds

An ESP is useful parameter about molecules reactive behavior, especially in intermolecular interactions and it indicates electron-rich (nucleophilic) and electron-poor (electrophilic) sites of molecules. The ESP maximum (minimum) value is equal to 61.04 (-5037) kcal/mol in the keto form of Favipiravir, and the maxima is localized in vicinity of H atom of aromatic N atom (Fig.3). The minimum is localized in vicinity of amid O and pyridine type N atoms. In this case of Lavumidine it is equal to 51.28 (-54.02) kcal/mol.

In the case of the cocrystal, the maximum is localized in vicinity of H atom of Lavumidine's -OH group. And The minimum is localized near to pyridine type N and amid O atoms of Favipiravir (Fig.3).

Frontier molecular orbitals (HOMO, LUMO), energy gap between them (ΔE), total energy (Etot), atomic charges on selected atoms (Qi), dipole moment (μ), electronegativity (χ), chemical hardness (η), chemical potential (μp), softness (σ) and electrophilicity index (ω) are considered as quantum chemical descriptors (QCP) in QSAR. According to Koopmans' theorem HOMO and LUMO are equal to ionization potential (I) and electron affinity (A), respectively. HOMO represents the electron-donating ability of molecules, and LUMO is the electron-acceptor ability of molecules in a series of related compounds. Energy gap (ΔE) considered as a stability index of chemical compounds. Therefore, the parameters mentioned above were calculated for both keto and enol tautomers of Favipiravir, Lavumidine and also for their cocrystal (Table 1). It is known that molecules with a small energy gap between (ΔE) HOMO and LUMO are more polarizable and have a higher chemical reactivity. According to Table 1, the co-crystal has a smaller energy gap between the boundary orbitals.

Table 1. QCP for both tautomer form of Favipiravir and Lamivudine and their cocrystal calculated by the B3LYP/def2-TZVP method in vacuum

Quantum chemical parameter	F (Enol)	F (keto)	L	Cocrystal
E_{HOMO}, eV	-7.23	-6.98	-6.15	-6.42
E_{LUMO}, eV	-2.45	-2.94	-0.75	-2.34
$\|\Delta E\| = E_{HOMO} - E_{LUMO}$, (eV)	4.78	4.04	5.4	4.08
Ionisation potentials, $I = - E_{HOMO}$, (eV)	7.23	6.98	6.15	6.42
Electron affinity, $A = - E_{LUMO}$, (eV)	2.45	2.94	0.75	2.34
Electronegativity, $\chi = (I + A)/2$ (eV)	4.84	4.96	3.45	4.38
Chemical hardness, $\eta = (I - A)/2$ (eV)	2.39	2.02	5.4	2.04
Chemical potential, $\mu_p = - (I + A)/2$ (eV)	-4.84	-4.96	-3.45	-4.38
Chemical softness, $s = 1/(2\eta)$ (eV^{-1})	0.20	0.24	0.09	0.24
Electrophilicity index, $w = \mu_p^2/2\eta$ (eV)	4.89	6.02	1.10	4.70
Dipole moment, μ (Debye)	5.78	5.99	6.49	13.82

**F(Enol)- enol tautomeric form of favipiravir, F (keto) - keto tautomeric form of favipiravir and L – lamivudine*

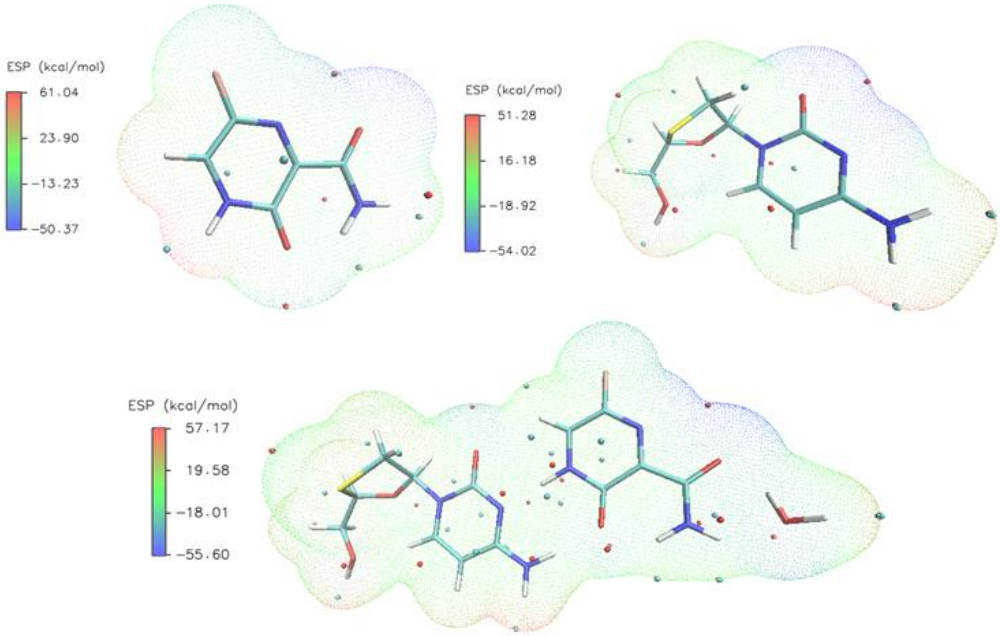

Fig.3. ESP surface for keto form of Favipiravir, Lavumidine and their cocrystal.

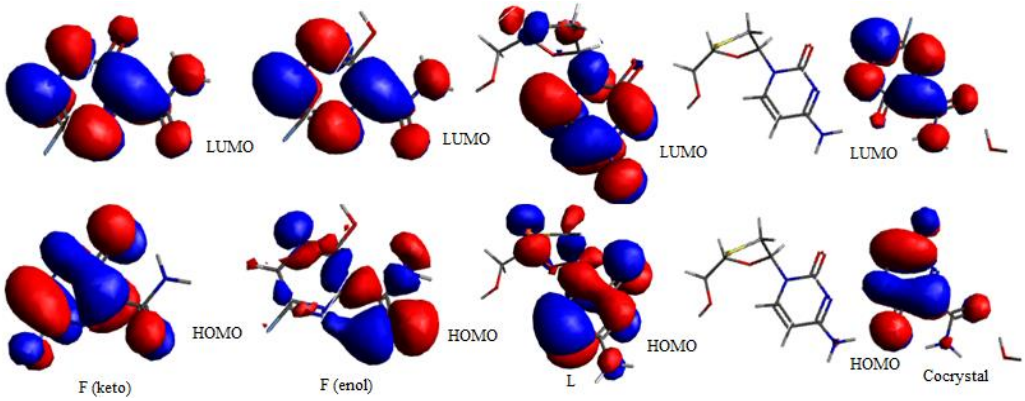

Fig.4. Frontier electron densities for keto form of Favipiravir, Lavumidine and their cocrystal.

NCI analysis shows presence of H-bond, steric effects and also Van-der-Waals interaction in cocrystal obtained by interaction of Favipiravir and Lavumidine (Fig.)

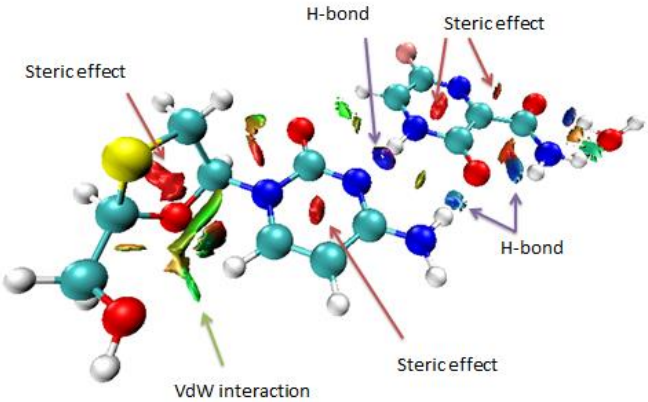

Fig.5. Non-covalent interactions in the cocrystal.

Conclusion.

Thus, the geometry of Favipiravir, Lavumidine and their cocrystal were fully optimized by B3LYP/def2-TZVP method and some quantum-chemical parameters have been calculated. The ESP surface minima and maxima were determined for the cocrystal and its main components. Furthermore, non-covalent interactions of cocrystal is visualized using MultiWFN and VMD program packages

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