DFT and TD-DFT Study of Favipiravir Tautomerism as RNA Polymerase Inhibitors: COVID-19

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Abstract: Favipiravir is an antiviral medication currently being trialled as a COVID-19 treatment. To help accelerate these efforts, we have performed a research for tautomers formations of favipiravir as possible RNA polymerase enzyme inhibitors and mitigating the virus ability. This study provides important electronic and optical properties of tautomers determined by density functional theory (DFT) and time-dependent density function theory (TD-DFT) calculations in gas phase and in water. A series of favipiravir derivatives was designed, and study the effect of the HOMO-LUMO energy gap on the efficacy of inhibitors. It has been determined that H-atom positions change and substituting fluorine (F) by hydroxyl (OH) group of tautomers affects the energy gap and dipole moment values. Among all compounds, the results have shown that Fb4 form with OH is most potent inhibitory activity in both gas phase and water. These investigations indicated that these tautomers could be potentially developed into drugs, but further investigations are still required to examine the cytotoxicity and consequent side reactions.

Keywords: COVID-19, Favipiravir, Tautomerism, Inhibition, TD-DFT

1. Introduction

Since the December 2019, novel coronavirus disease (COVID-19) was first identified amid outbreak of respiratory illness cases in Wuhan city, Hubei province China and made several serious problems to the global health [1-4]. Without any available approved antiviral, considerable efforts have been done to examine available drugs to rapid detection of a way for pharmacotherapy [1,3].

Early exploratory studies show that inhibitors of enzymatic activity may be effective in treating COVID-19 [5,6]. Favipiravir is a broad antiviral drug (such as Arenavirus, Bunyavirus, Favivirus, Alphavirus, Norovirus, and Ebolavirus) belongs to the pyrazine carboxamide family, developed by FUJIFILM of Japan with activity against influenza viruses [7,8]. Recently has shown promising results in the treatment of COVID-19 patients in the clinical trials [9], as it is thought to inhibit the RNA-dependent RNA polymerase enzyme, and mitigating the virus ability to spread from one cell to another [10-12].

While the use of favipiravir drug, uncertainty remains about its safety and effectiveness [12], therefore, tautomers have been used in the synthesis some favipiravir compounds. The transfer of the protons and electrons from one place to another in an intramolecular changes the electronic structure and, hence, variety the properties, a reaction which involves proton transfer is called a tautomerism [13-15]. As a result, the tautomeric forms differ in shape, and double bonds pattern. Biological activity is one of the properties that are heavily affected by the proton transfer, the vital importance of knowing the tautomers states has been underlined by many authors [7]. The energy gap previously described can be used of drugs to investigate structure activity, and molecular
properties [16]. The energy gap of the inhibitors will also be influential in determining drug cytotoxicity and side effects in the body [17].

In this study, it is possible change the molecular properties of drugs and makes them possible candidates by changes in the band gap energy, which specifies the molecular reactivity of the drug. We applied density functional theory (DFT) and time-dependent density functional theory (TD-DFT) methods to tautomers formations of favipiravir based on the H-atom movement, to shed light on geometric, electronic and optical properties like the energy gap (Eg), dipole moments (DM), electronic spectrum, highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) to candidate the best.

2. Computational Methodology

The computational model of favipiravir consists of 5 carbon, 3 nitrogen, 2 oxygen, 1 fluorine atoms with 4 hydrogen atoms in ends [18,19]. Structures of available tautomers of favipiravir have been analyzed by performing density functional theory (DFT) investigations at the level B3LYP functional and the 6–32G basis set as implemented in the Gaussian 09W software [20,21]. The values including energy levels of (EHOMO and ELUMO), the energy gap (\(E_g = E_{LUMO} - E_{HOMO}\)) [22], total energy (E_total), and dipole moments (DM) have been obtained for the optimized structures. The UV–Vis spectra, maximum absorption wavelengths (\(\lambda_{max}\)) and oscillator strengths (f) of the compounds were investigated with the time-dependent DFT (TD-DFT). We also computed these parameters for tautomers, by substituting fluorine (F) by hydroxyl (OH) group (Figure 1) for the hope of better understanding and possible application for COVID-19 Patients. All the calculations in this work were studied in the gas and water phase, to evaluate the reactivity and effect of water solvent on the obtained parameters [23,24].

![Chemical structure of favipiravir (Fa1), and optimized structures of tautomers forms based on the H-atom movement.](image)

3. Results and discussion

The tautomerism is one of the most studied cases, both theoretically and experimentally. We have optimized and geometric analysis of four different tautomers for each configuration of favipiravir by DFT method with B3LYP functional and 6-31G basis set. Intra or intermolecular hydrogen bonding is also an important parameter of molecule, which usually leads to shortening of the C–OH bond compared to bond length of C–F, for compounds studied. Based on the gotten
results, the figure and the bond lengths in Å unit in different positions of tautomeric structures have been illustrated in Figure 2. It is noted that number of atoms are fixed, but movement of H-atom among N and O atomic sites could bring significant characteristics for compounds.

Figure 2. The bond lengths in angstrom unit of the investigated compounds at B3LYP/6-31G level of theory.

The relationship between the drug properties and various biological processes is based on electronic properties of compounds. There is strong evidence from the literature that the energy gap and dipole moment are good inherent indicators of the transport or binding ability of drugs [23-26]. The energy gap is the dominant factor for determining the inhibitory efficacy of favipiravir, the dipole moment is roughly less influential than the energy gap. The fluorine substitution by hydroxil group leads to change the energy gap (Eg), which is energy difference between the HOMO and LUMO levels that in turn alters the electronic properties.

The energy gap (Eg) of the original favipiravir molecule (Fa1) equal to 4.426 eV. The Eg usually decrease with the tautomers, where Eg equal to 4.209 eV of Fa2 and 3.854 eV with Fa3. The Eg gives the minimum values since 3.787 eV with Fa4. Whereas when substitution F by OH, the Eg are changed to 4.591, 4.349, 3.838 eV for Fb1, Fb2, and Fb3, respectively. The Eg value 3.456 eV of Fb4 indicates to the better improved of favipiravir molecule. From the values of dipole moments (DM), we note that the compounds have large dipole moment and this is a basic criteria for the interaction between drug and receptor. It is essential to analyze the density of state (DOS) and the HOMO and LUMO distribution patterns of the tautomers formations before and after substituting F atoms with OH group to more know the changes in molecular properties.

The DOS with various sites of H-atom, we observed that the DOS structure and electronic band gap are affected by changing the locations of the H-atom. Where the origin of the energy gap depends on the structural configuration of H-atom and the double bond of tautomers. Figure 3 show the HOMO and LUMO distribution and the DOS analysis which consists of the energy difference for the HOMO-LUMO, for detect the effects of tautomerism process on the molecular orbitals of all...
systems under study. Where before substituting F atom with OH, the HOMO and LUMO are localized in all atoms except on F atom of Fa1, Fa2, and Fa3, this is clear from the spatial charge distribution, whereas HOMO localized in all atoms of Fa4 molecule. While after substituting F atom with OH, the HOMO and LUMO are localized on all the atoms of except on OH group of Fb1, but HOMO localized on all the atoms of Fb2, Fb3, and Fb4.

Based on the computational method, the total energies data would be of importance of assessment of the stability of favipiravir compounds and for choosing of the greatest stable structures. All the parameters of the compounds studied in the gas phase and water solvent in Table 1.

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|        | HOMO                  | DOSs                  | LUMO                  |
|--------|-----------------------|-----------------------|-----------------------|
| Fa1    | HOMO                  | DOSs                  | LUMO                  |
|        | Gap = 4.426 eV        |                       |                       |
| Fa2    | HOMO                  | DOSs                  | LUMO                  |
|        | Gap = 4.209 eV        |                       |                       |
Fa3

\[
\text{HOMO - LUMO Gap} = 3.854 \text{ eV}
\]

Fa4

\[
\text{HOMO - LUMO Gap} = 3.787 \text{ eV}
\]

Fb1

\[
\text{HOMO - LUMO Gap} = 4.591 \text{ eV}
\]

Fb2

\[
\text{HOMO - LUMO Gap} = 4.349 \text{ eV}
\]
Figure 3. Density of states (DOS), as well as HOMO–LUMO distribution of the investigated compounds at B3LYP/6-31G level of theory; from the left-occupied orbitals, from the right-virtual orbitals.

Table 1

The HOMO energies (E_HOMO), LUMO energies (E_LUMO), energy gap (E_g), dipole moment (DM), and total energy (E_total) were calculated at B3LYP/6-31G level of theory for compounds under study in the gas phase and water solvent.

| Property     | Fa1     | Fa2     | Fa3     | Fa4     | Fb1     | Fb2     | Fb3     | Fb4     |
|--------------|---------|---------|---------|---------|---------|---------|---------|---------|
| **Gas**      |         |         |         |         |         |         |         |         |
| HOMO (eV)    | -6.979  | -7.108  | -6.892  | -6.843  | -6.810  | -6.920  | -6.519  | -6.270  |
| LUMO (eV)    | -2.553  | -2.899  | -3.038  | -3.056  | -2.219  | -2.571  | -2.681  | -2.814  |
| E_g (eV)     | 4.426   | 4.209   | 3.854   | 3.787   | 4.591   | 4.349   | 3.838   | 3.456   |
| DM (Debye)   | 6.373   | 6.100   | 6.599   | 5.260   | 3.927   | 5.265   | 7.896   | 5.551   |
| E_total (eV) | -16524.405 | -16523.498 | -16524.648 | -16523.643 | -15871.063 | -15870.097 | -15870.927 | -15870.156 |
| **Water**    |         |         |         |         |         |         |         |         |
| HOMO (eV)    | -7.265  | -7.305  | -6.875  | -6.726  | -6.822  | -6.820  | -6.361  | -6.193  |
| LUMO (eV)    | -2.478  | -2.634  | -2.862  | -2.891  | -2.232  | -2.385  | -2.628  | -2.704  |
| E_g (eV)     | 4.787   | 4.671   | 4.013   | 3.835   | 4.590   | 4.435   | 3.733   | 3.489   |
| DM (Debye)   | 8.432   | 7.612   | 8.882   | 7.755   | 5.361   | 6.676   | 10.712  | 8.401   |
| E_total (eV) | -16524.947 | -16524.011 | -16524.341 | -16524.294 | -15871.577 | -15870.666 | -15871.829 | -15870.878 |

The UV–Vis spectra, maximum absorption wavelengths (λ_{max}) and oscillator strengths (f) for tautomers before and after replacing F atom with OH were simulated with TD-DFT at B3LYP/6-31G level of theory using the gas-phase optimized geometries. The absorption bands
were centered at 297.45-374.98 nm range for F and OH-compound. The simulated UV–Vis spectra agree well with the interaction energies and HOMO-LUMO gap. All the molecular results of the electronic spectrum are collected in Table 2. The UV–Vis spectra for all compounds are shown in Figure 4.

Table 2

| Property | Fa1  | Fa2  | Fa3  | Fa4  | Fb1  | Fb2  | Fb3  | Fb4  |
|----------|------|------|------|------|------|------|------|------|
| \(\lambda_{\text{max}}\) (nm) | 306.90 | 300.44 | 345.80 | 332.94 | 307.18 | 297.45 | 363.00 | 374.98 |
| f        | 0.0054 | 0.0720 | 0.0500 | 0.0613 | 0.0102 | 0.0761 | 0.0826 | 0.0966 |

Figure 4. Simulated UV-Vis spectra of the compounds in the gas phase.

The obtained values of tautomers indicate that Fb4 with OH could interact in stronger mode than other Fa and Fb structures, however, these parameters could be fully validated only by further experimental studies to synthesize them.

4. Conclusion

In summary, we studied the synthesis, electronic and optical features of favipiravir compounds by using DFT and TD-DFT calculations. Depending on positions of H-atom, change in the electronic properties are observed. From the obtained results, the inhibitory efficacy of the RNA polymerase enzyme by a tautomers of drug has been shown to be mainly determined by the HOMO-LUMO energy gap of the inhibitors, as the energy gap of the inhibitors is an inherent chemical reactivity, with lesser dependencies on the dipole moment. Fb4 is the most active tautomer based on the energy gap values and the good stable based on the structural analysis results with hydroxyl (OH) group, the substitutional hydroxyl would be promising candidate. Finally, favipiravir could be considered for showing the inhibitory efficacy, but further investigations are still required to examine different sides of favipiravir use in COVID-19.

References

[1] Harismah K, Mirzaei M. Favipiravir: Structural Analysis and Activity against COVID-19. Adv J Chem Sect B Nat Prod Med Chem. 2020;2(2):55–60.

[2] Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir
for COVID-19: an open-label control study. Engineering. 2020;

[3] Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv. 2020;

[4] Nyarko RO, Boateng E, Kahwa I, Boateng PO. A Comparison analysis on remdesivir, favipiravir, hydroxychloroquine, chloroquine and azithromycin in the treatment of coronavirus disease 2019 (Covid-19)-A Review. 2020;

[5] Guo Q, Xu M, Guo S, Zhu F, Xie Y, Shen J. The complete synthesis of favipiravir from 2-aminopyrazine. Chem Pap. 2019;73(5):1043–51.

[6] Niloofa R, de zoysa I, Seneviratne PS, Abeysuriya V, de Mel S. Favipiravir in Covid-19. 2020 Mar 20;19:143–5.

[7] Antonov L. Favipiravir tautomerism: a short theoretical report. 2020;

[8] Parłak C, Alver Ö, Şenyel M. Computational study on favipiravir adsorption onto undoped- and silicon-decorated C60 fullerenes. J Theor Comput Chem. 2017;16(02):1750011.

[9] da Silva G. Protonation, Tautomerism, and Base Pairing of the Antiviral Favipiravir (T-705). 2020;

[10] Du Y, Chen X. Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. Clin Pharmacol Ther. 2020;

[11] Khambholja K, Asudani D. Potential repurposing of Favipiravir in COVID-19 outbreak based on current evidence. Travel Med Infect Dis. 2020;101710.

[12] Arab-Zozani M, Hassanipour S, GHoddoosi-Nejad Dj. Favipiravir for treating novel coronavirus (COVID-19) patients: protocol for a systematic review and meta-analysis of controlled trials. medRxiv. 2020;

[13] Martin YC. Let’s not forget tautomers. J Comput Aided Mol Des. 2009;23(10):693.

[14] Martin YC. Experimental and pKa prediction aspects of tautomerism of drug-like molecules. Drug Discov Today Technol. 2018;27:59–64.

[15] Katritzky AR, Hall CD, El-Gendy BE-DM, Draghici B. Tautomerism in drug discovery. J Comput Aided Mol Des. 2010;24(6–7):475–84.

[16] Fong C. Role of stable free radicals in conjugated antioxidant and cytotoxicity treatment of triple negative breast cancer. 2018;

[17] Fong C. Toxicology of platinum anticancer drugs: oxidative stress and antioxidant effect of stable free radical Pt-nitroxides. 2019;

[18] Rhyman L, Tursun M, Abdallah HH, Choong YS, Parłak C, Kharkar P, et al. Theoretical investigation of the derivatives of favipiravir (T-705) as potential drugs for Ebola virus. Phys Sci Rev. 2018;3(9).

[19] Liu W, Zhu H-M, Niu G-J, Shi E-Z, Chen J, Sun B, et al. Synthesis, modification and docking studies of 5-sulfonyl isatin derivatives as SARS-CoV 3C-like protease inhibitors. Bioorg Med Chem. 2014;22(1):292–302.

[20] Parłak C, Alver Ö, Ramasami P. Adsorption Mechanisms of 6-Chloro-3-Hydroxy-2-Pyrazinecarboxamide on Pristine, Si-and Al-Doped C 60 Fullerenes: A DFT Study. J Clust
Sci. 2017;28(5):2645–52.

[21] Stephens PJ, Devlin FJ, Chabalowski CF, Frisch MJ. J. Baker, J. Andzelm, M. Muir, PR Taylor. Chem Phys J Phys Chem. 1994;98:11623.

[22] Fong C. Inhibition of COVID-2019 3C-like protease: structure activity relationship using quantum mechanics. Eigenenergy, Adelaide, Australia; 2020.

[23] Fong C. Comparison of choline blood brain barrier and neuronal transport and anticholinesterase inhibitory properties of potential cationic Alzheimers disease drugs. Eigenenergy, Adelaide, Australia; 2020.

[24] Fong CW. Permeability of the blood–brain barrier: molecular mechanism of transport of drugs and physiologically important compounds. J Membr Biol. 2015;248(4):651–69.

[25] Fong C. The extravascular penetration of tirapazamine into tumours: a predictive model of the transport and efficacy of hypoxia specific cytotoxic analogues and the potential use of cucurbiturils to facilitate delivery. 2017;

[26] Fong C. Screening anti-colorectal cancer drugs: free radical chemotherapy. 2019;