

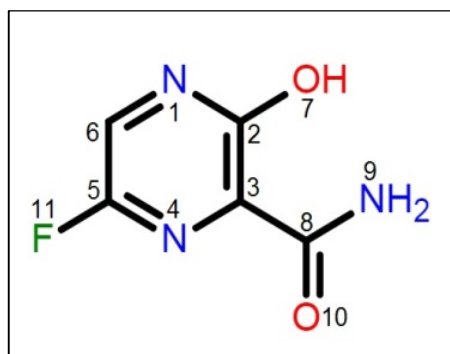


Favipiravir: Structural Analysis and Activity against COVID-19

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ABSTRACT

Within this work, we have performed an *in silico* research for structural analysis of Favipiravir and its activity against COVID-19. To this aim, tautomers formations of Favipiravir have been first examined and found that four tautomeric structures could be considered as ligands obtained by density functional theory (DFT) calculations. The related protease and polymerase macromolecules to COVID-19 have been assigned as targets to examine the activity of ligands by Molecular Docking simulations. The results indicated that each of four ligands could interact with each of targets with different properties. F3 is the most stable tautomer and F1 is most active ligand against macromolecules. It has been found that the activity of ligands are more favorable for protease than polymerase target, but the ligand...target interacting complexes are not so much strong regarding low values of binding energies. Qualitative representations of ligand...target interactions also indicated different environments of interaction for complex formations. It is noted that further investigations are still required to examine the dominant activity of Favipiravir against COVID-19.

Introduction

Since the late of year 2019, novel coronavirus disease (COVID-19) has been spread almost all around the world and made several serious problems to the public health [1]. Without any available approved antiviral, agent several attempts have been dedicated to explore medicinal compounds for supportive care of this

infection [2]. In addition to explore novel compounds, examining available drugs is an important task to rapid detection of a way for pharmacotherapy of COVID-19. By introducing protease structure of COVID-19 in the early of year 2020 [3], considerable efforts have been done to examine the efficacy of available related drugs on the enzymatic activity [4]. Moreover, knowing

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mechanism of action of ligand...target complex is also an important task to move further in drug design and discovery processes [5-8].

Within this work, the efficacy of Favipiravir (Fig. 1) on COVID-19 growth prevention has been examined by *in silico* methods. Structural analysis of Favipiravir has been done prior to exploring its biological efficacy on the related protease and polymerase enzymes to COVID-19. Favipiravir is an antiviral drug being developed by Fujifilm group of Japan with activity against many RNA viruses [9]. It has been also examined for different types of influenza in the last years [10]. In very much recent works, Favipiravir has been studied for experimental treatments of COVID-19, in which it has been suggested as effective drug for the purpose [11]. To this aim, a systematic

investigation has been done in this work to analyze the structural properties of Favipiravir in addition to exploring its biological activity. Tautomeric conformational changes are very much common in the cyclic organic compounds [12-15], in which Favipiravir could also undergo tautomerism processes (Fig. 1). Therefore, structures of all tautomeric forms of Favipiravir have been investigated based on quantum chemical computations and then the biological activity of each tautomer has been examined by Molecular Docking simulations of related protease and polymerase to COVID-19. It is worth to note that *in silico* environment could provide molecular scale computations to reveal insightful information about the complicated ligand...target interacting complexes [16-20].

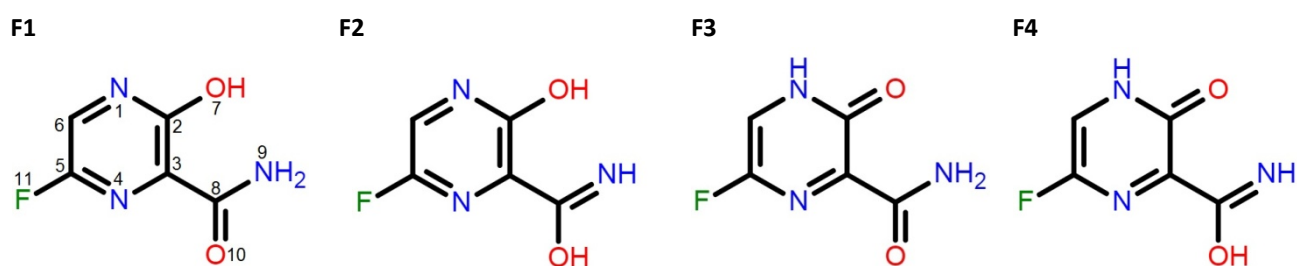


Fig. 1. The tautomeric structures of Favipiravir represented by F1-F4 based on the H atom movement.

Materials and Methods

Within this work, *in silico* investigations have been performed to explore possible formation of ligand...target interacting complexes of Favipiravir with each of the related protease and polymerase enzymes of COVID-19. In the first step, structures of available tautomers of Favipiravir (Fig. 1) have been analyzed by performing density functional theory (DFT) calculations at the B3LYP/6-31G* theoretical level as implemented in the Gaussian program [21]. Earlier works indicated that the molecular properties could be very well evaluated by the quantum chemical computations [22-28]. The values including total energy (E), relative energy of stabilization (ΔE), energy levels of the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO), and the

energy gap (EG) have been obtained for the optimized structures (Table 1 and Fig. 2). In the next step, Molecular Docking simulations have been performed to investigate possible formations of ligand...target interacting complexes. Each tautomer has been assigned for the ligand counterpart and two pdb files including 6LU7 for the COVID-19 main protease [3] and 6NUR for SARS-Coronavirus polymerase [29] have been assigned for the target counterpart. Molecular Docking simulations using the AutoDock4 program [30] have been performed by employing 300 conformational exploration of Genetic Algorithms. Because of sizes of pdb structures, the grid box has been set 70×70×70 for 6LU7 and 100×100×100 for 6NUR. The obtained values of binding energy (EB) and inhibition

constant (KI) could show the potency of each ligand to inhibit the target activity (Table 1). The qualitative representation of ligand...target interacting complexes (Fig. 3) could reveal

insightful information about the characteristics of biological activity for each ligand against the interacting target based on the molecular counterparts [31-33].

Table 1: The molecular properties*

Property	F1	F2	F3	F4
E kcal/mol	-380886	-380871	-380891	-380876
delta-E kcal/mol	5	20	0	15
LUMO eV	-2.24	-2.23	-2.66	-2.69
HOMO eV	-6.98	-7.05	-6.71	-6.62
EG eV	4.74	4.82	4.05	3.93
DM Debye	3.45	0.74	5.91	4.78
Ligand-Protease:				
EB kcal/mol	-4.67	-4.40	-4.16	-4.09
KI uM	377	599	892	1000
Ligand-Polymerase:				
EB kcal/mol	-4.25	-4.09	-3.92	-4.02
KI uM	766	1000	1330	1130

*See Figs. 1 and 3 for the models.

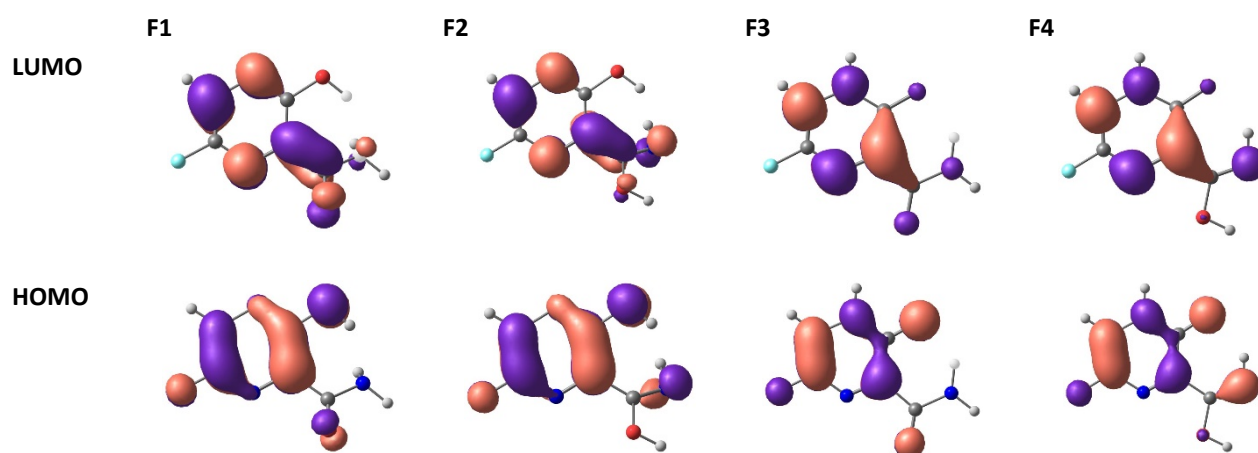


Fig. 2. The LUMO and HOMO distribution patterns.

Results and Discussion

Structural analysis of Favipiravir has been done by exploring tautomers formations (Fig. 1). Four tautomers have been seen possible for Favipiravir, in which their stability could be different regarding the values of total energy (E) of Table 1. The results indicate that F3 is the most stable structure and the next one is F1 by 5 kcal/mol difference in the stability level (delta-E). F4 and F2 are the next tautomers regarding lower stability than the

former two ones. These tautomers could be available if the required energy for tautomer formation are supplied by other resources such as intermolecular interactions and bonding. Therefore, it is very much important to recognize such structures prior to exploring their activity in biological media. For small molecules, tautomerism could be available easier than the large molecules, in which Favipiravir is almost a small heterocyclic molecule with ability of

tautomer formations. The values of energy levels for the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) indicate that the internal molecular properties could detect effects of tautomerism process, as shown by different values for the obtained levels of molecular orbitals. The HOMO and LUMO distribution patterns also show effects of tautomers formations (Fig. 2). The values of energy gap (EG), which is energy difference between the HOMO and LUMO levels, also

indicate that the gap between two levels also detect the effects of such molecular conformation change. It is noted that number of atoms are fixed in the tautomers, but movement of H atom among N and O atomic sites could bring significant characteristics for the evaluated tautomeric structures. The trend could be very much better seen by the values of dipole moments (DM), in which different orientations of electronic directions could be detected by different values of DM.

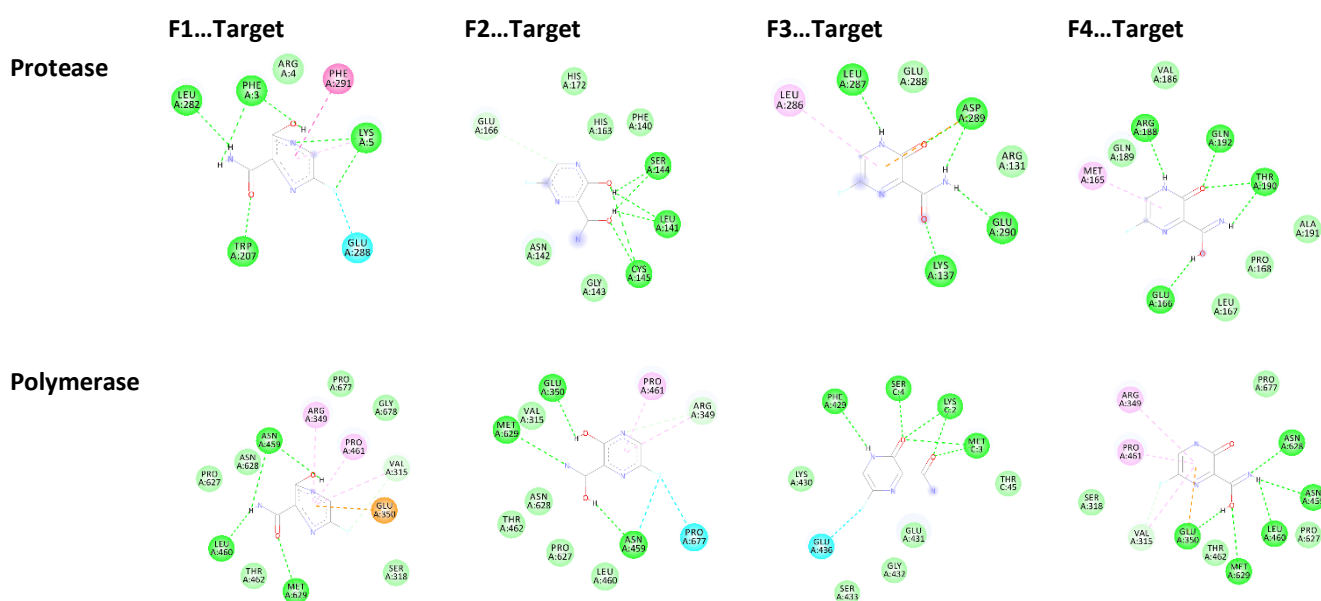


Fig. 3. The ligand...target interacting complexes.

Activity of Favipiravir against COVID-19 has been done by performing Molecular Docking simulations using the tautomeric ligands and available protease (6LU7) and polymerase (6NUR) targeting enzymes. The obtained values of binding energy (EB) and inhibition constant (KI) are used to recognize the quantitative efficacy of each ligand on each target (Table 1) and the molecular representations of ligand...target interacting complexes (Fig. 3) could show the qualitative aspects of Favipiravir against COVID-19. The obtained values of EB and KI indicate that F1 could interact with each of protease and polymerase in stronger mode than other F structures. Comparing the EB values for two macromolecules could show

that protease is somehow better target for F1 than polymerase. Other F structures are also interacting with the targets but with lower strength of ligand...target complex formations. The point is that overall interactions of F ligands are stronger for protease than polymerase target but with almost low strength by the EB values. The qualitative representation of ligand...target interactions also show different interacting environments for the F tautomers against each of the protease and polymerase macromolecular targets. This trend could show the importance of knowledge about possible tautomeric formations of ligands for their activity against macromolecular targets.

Conclusion

By the obtained results of this work for structural analysis of Favipiravir and its activity against COVID-19, some concluding remarks could be summarized. First, each of four investigated tautomeric ligands could interact with each of protease and polymerase targets with different interacting properties. Second, F3 is the most stable tautomer based on the structural analysis results and F1 is the most active ligand against macromolecules based on the Molecular Docking simulations. Third, the activity of ligands are more favorable for protease than polymerase target. Fourth, the qualitative representations of

ligand...target interactions indicated different environments of interactions for complex formations. And finally, Favipiravir could be considered for showing activity against COVID-19 but with low binding strength, which means that further investigations are still required to examine different sides of such proposed pharmacotherapy application.

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