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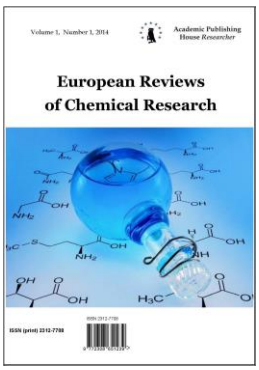

Articles

Molecular Docking Study of Primaquine-Favipiravir Based Compounds as Potential Inhibitors of COVID-19 Main Protease

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Abstract

The continuous search for drugs that can combat COVID-19 virus is very important in a bid to save lives and address failing economies. Schiff bases and amide compounds derived from the fusion of primaquine (a 4-aminoqinoline antimalarial) and favipiravir are hereby reported because of suitable synthetic approaches and are investigated for their potential as drug candidates against the virus. The molecular docking results using iGEMDOCK and LeDock showed that the compounds had better interaction with the protease protein of the coronavirus (6LU7) as they displayed better scores than the standard drugs used in the study (chloroquine and favipiravir). The high binding affinity could be as a result of the fusion of both drug candidates. The docking results were analyzed using Discovery Studio and PyMOL. The druglikeness showed that they qualify as oral drug candidates, hence these compounds could serve as potential inhibitors of COVID-19, subject to further clinical and pre-clinical probes.

Keywords: COVID-19 inhibitors, primaquine, favipiravir, drug-likeness, Schiff bases, amides.

1. Introduction

Coronaviruses were first reported in 1947 (Bailey et al., 1949), since then several viruses under the same family have been discovered and reported, they were first known to infect animals in a very severe manner (Pillaiyar et al., 2016). However, their recent infection on man has triggered serious interest in the understanding of these classes of viruses as well as ways to deal with them, especially as they are associated with deadly diseases from severe acute respiratory syndrome (SARS). These viruses are members of two subfamilies coronaviridae belonging to the order Nidovirales.

The discovery of a new strain of coronaviruses responsible for an outbreak in Wuhan, China alerted health related bodies to take up measures towards curtailing the outbreak. The outbreak,

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which was later considered to be one of the Public Health Emergencies of International Concern (PHEIC) by WHO, is reported to have spread to six (6) continents with more than 18.5 million infections in 188 countries and with more than 700,000 deaths (Aljazeera, 2020). It has also caused a lot of economic problems resulting from the lockdown enforced by the governments of affected countries. The organization reported that the risk assessment of the outbreak is very high and named the virus responsible for the infection of the disease. Currently, there are no established drugs or therapies for COVID-19, although WHO reports the commencement of the first vaccine trial in China. Most of the measures implemented in various countries against the infection are mainly preventive as well as supportive. In a bid to deal with the COVID-19 infection, several studies are been undertaken. Most of these studies relate to the use of existing antiviral drugs against the infection. For instance opinavir/ritonavir, an anti-HIV drug has been tested against the virus (Asai et al., 2020). Amidst the trials, several studies suggest that chloroquine shows potential in being effective against the virus particularly SARS–CoV (Vincent et al., 2005, Cao et al., 2020). In addition to this, it has been also reported to display considerable activity on patients infected with the COVID-19. Despite the promising potential of chloroquine, it is yet to be accepted as well as approved as an efficient drug against COVID-19.

4-Aminoquinolines have shown great potential in dealing with several infections. Members of this group like chloroquine, amodiaquine and primaquine are frontline drugs in the treatment of malaria caused by several strains of plasmodium (Deshpande, Kuppast, 2016). This is due to the presence of a common quinoline pharmacophore, which is reported to bind to heme in the parasite thus inhibiting hematin formation and causing the death of the malaria parasite. Several studies also demonstrated that 4-aminoquinoline drugs were able to interfere as well as inhibit DNA and RNA synthesis in microorganisms, inhibition of RNA synthesis is very important in dealing with viral infections. Primaquine is a quinoline based antimalarial drug which also serves as a therapy for *Pneumocystis* pneumonia. It is specifically used to prevent a relapse of malaria elicited by plasmodium vivax and ovale. It is combined with quinine or chloroquine during administration (Baird, Reickmann, 2003). It has been recommended by the WHO for use in reducing transmission in control of *P. falciparum* infection.

Favipiravir, a derivative of pyridine carboxamide is an antiviral drug that has promising prospects for combating many RNA viruses, it has displayed promising action against influenza, west Nile, flaviviruses, zika and ebola virus (Furutaa et al., 2009). Recently, it was reported to be one of the frontline medication for coronavirus disease and is presently undergoing clinical trials (Chen et al., 2020, Dong et al., 2020). Several studies concerning other viral infections suggest that it acts as a purine nucleoside or purine during viral RNA replication (Furuta et al., 2005).

Several intensive research efforts are being devoted to deal with COVID-19 pandemic, some of which include the rational design and preparations of novel drugs, and the optimization of existing drugs. This is achieved by fusing them with other drugs of known activity or compounds having units that are known to exhibit biological activity, this strategy, known as hybridization is quite attractive. The result of the fusion is a hybrid molecule with additional structural features exhibiting diverse biological roles and additional bio-activity (Sashidhara et al., 2012).

Primaquine, as mentioned earlier, is part of the family of quinoline antimalarial. The compounds in this family have a common quinoline structure and exhibit similar activities against malaria and other ailments. Although chloroquine is the most widely used among the group, other members show similar and comparable biological activity, hence most times they are combined with chloroquine to increase its activity or deal with parasitic resistance (D'Alessandro et al., 2020). Primaquine, an aminoqinoline antimalarial drug, has been reported to display similar antiviral activity like chloroquine. Several reports also reveal that it inhibits protein synthesis in virus infected cells (Kajal et al., 2013). Favipiravir, on the other hand, is promising as it is reported to show reasonable activity against the coronavirus so much that it is undergoing clinical trials.

Schiff bases refer to compounds containing –C=N- (imine) functional group, they are synthesized through condensation of primary amines and carbonyl compounds. They are widely used organic compound and have applications in analytical, catalytic, and inorganic chemistry (Dhar, Taploo, 1982, Przybylski et al., 2009). In the medicinal and pharmaceutical fields, they have varied applications as they exhibit several biological activities, some of which includes antimicrobial, anticonvulsant, antitubercular activities (Aboul-Fadl et al., 2003, Chaubey, Pandeya, 2012, Ejelonu et al., 2018a, Ejelonu et al., 2018b). The nitrogen atom in Schiff bases is reported to

bond via hydrogen bond to the centre of cell constituents and impedes with normal cell processes (Boonen et al., 2012). This could lead to improved activity in the selected hybrid compounds. Amides are also very important in medicinal chemistry as many known drugs possess the amide functional group. Several important amide drugs include lidocaine, oseltamivir, sildenafil, cefotiam, paracetamol. They are known to interfere with biological processes within the cells of microorganisms.

Molecular docking is a computer-aided drug discovery/design (CADD) method used to obtain relevant information about the interaction of ligands (drugs) with biological cells via their respective receptors/proteins. Besides, it can, together with adsorption, distribution, metabolism and excretion/toxicity properties (ADME/Tox) provide relevant data that are useful for the prediction of the drug-like properties of any compound. It provides an opportunity for the identification of the most probable binding mode as well as affinity; beyond this, it gives room for better understanding of the molecular mechanism and biochemical pathways for such interaction (Chen et al., 2017, Olanrewaju et al., 2020, Metibemu et al., 2020). Therefore, this study seeks to perform molecular docking and drug-likeness on hybrid compounds; Schiff bases (PFB) and amides (PFA) obtained from the fusion of primaquine and favipiravir as drug candidates against coronavirus disease. It is expected that the hybrid candidates will display excellent bioavailability and bioactivity different from the drugs selected for this study. This is geared towards developing drug candidates that are more effective in dealing with the coronavirus. The modeled compounds are to be docked with the protease protein of the coronavirus downloaded from the protein data bank with code name 6LU7. The protease structure of this virus our target for the drug design as several antiviral drugs act by inhibiting the proteolytic maturation of viruses. Chloroquine and Favipiravir are used as standards for comparison in this study, since they are leading drug candidates for combating COVID-19.

2. Results

2.1. Chemistry

The proposed method for the synthesis of the compounds is thus:

a. The favipiravir is reduced to an aldehyde, the product undergoes a condensation reaction with primaquine to form Schiff bases (Figure 1).

b. Favipiravir is hydrolyzed to a carboxylic acid, which reacts with primaquine to form an amide via condensation (Figure 2).

Schiff bases

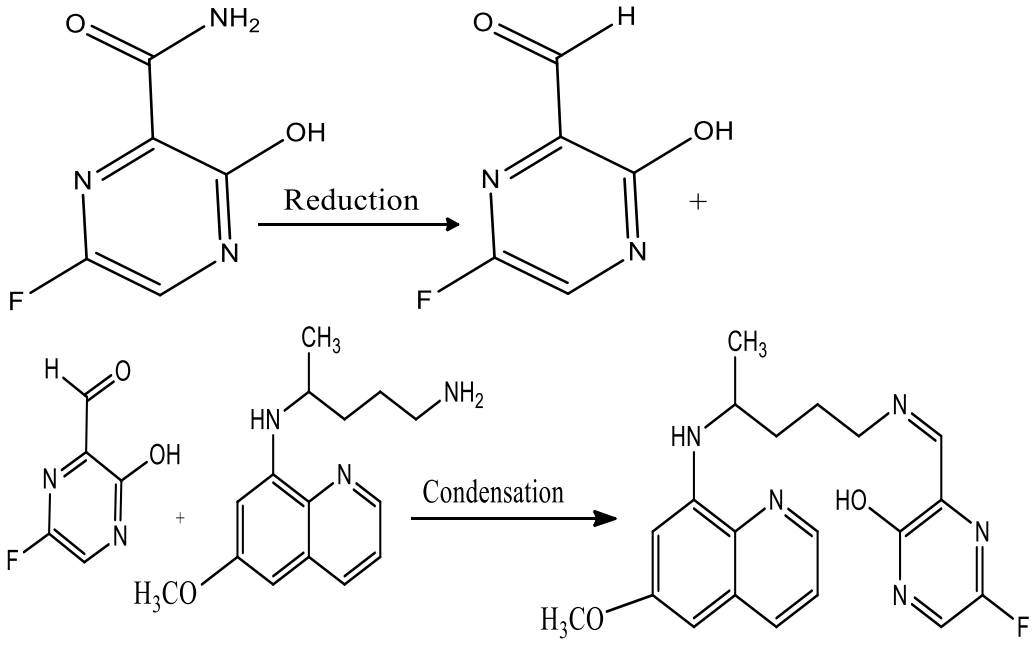


Fig. 1. Synthetic route for the Schiff bases

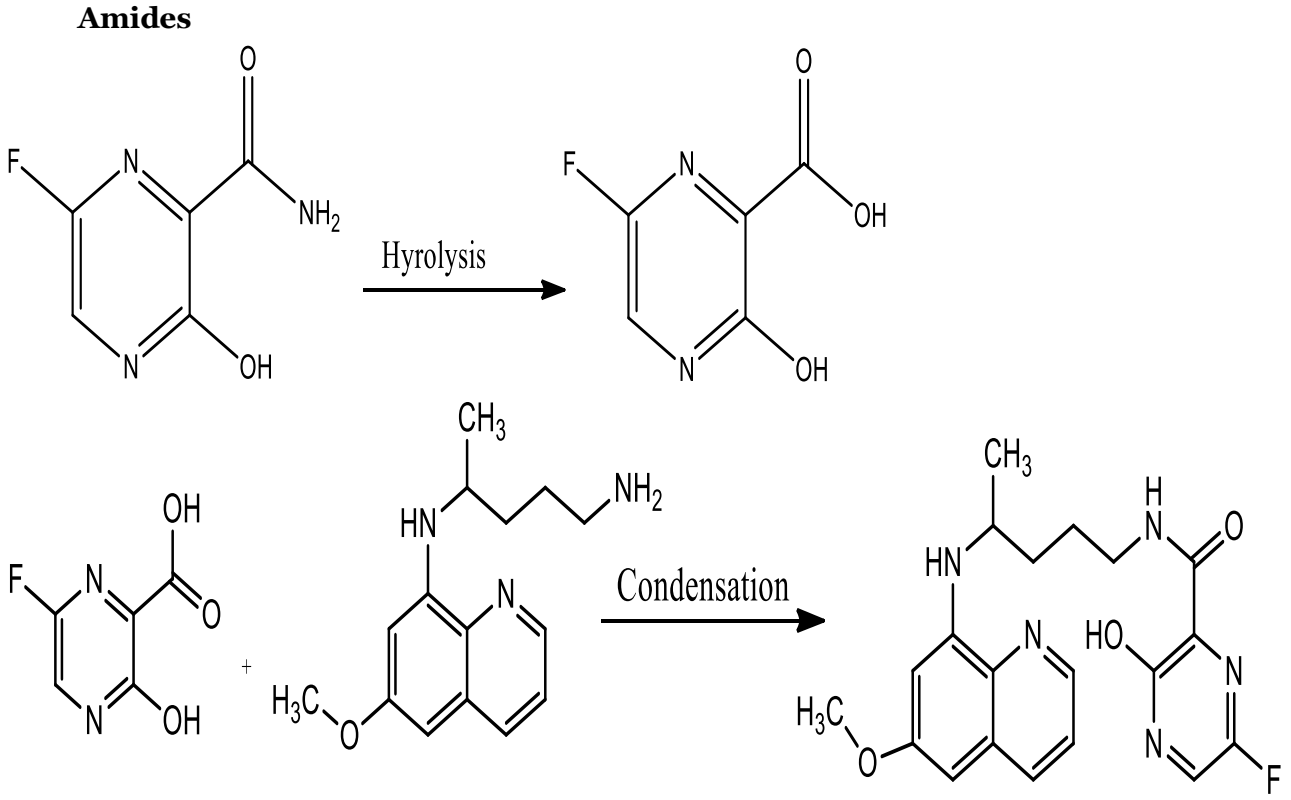
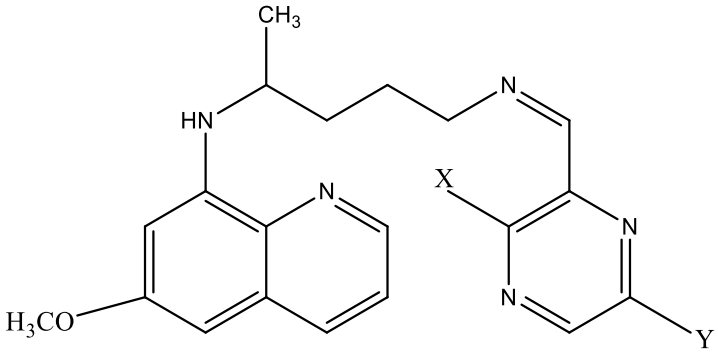


Fig. 2. Proposed method for the synthesis of amide compounds

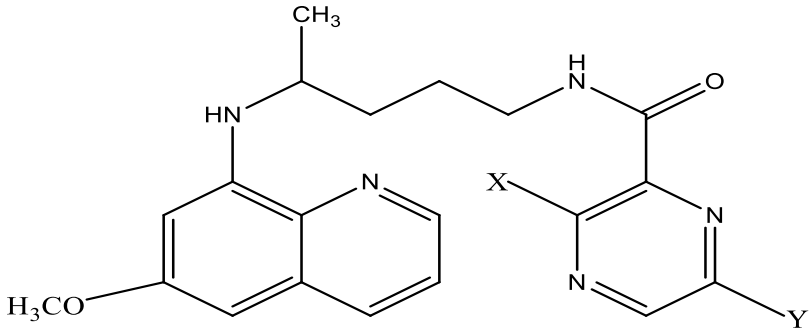
Certain structural changes were made to both the Schiff bases and amides shown in Figure 1 and Figure 2 by changing the substituents to produce different compounds with the same basic pharmacophore. This is an effort to study the effect of the substituents on the pharmacophore of the hybrid compounds. The structures of the compounds employed in this study are shown (Figure 3).

(A)



(*Z*)-N^1-((6-fluoro-3-methylpyrazin-2-yl)methylene)-N^4-(6-methoxyquinolin-8-yl)pentane-1,4-diamine derivatives

(B)



6-fluoro-3-hydroxy-*N*-(4-((6-methoxyquinolin-8-yl)amino)pentyl)pyrazine-2-carboxamide derivatives
X = OH, H and Y = F, Cl

Fig. 3. Structures of Primaquine-Favipiravir Schiff bases and Amides

(A) Schiff bases PF1B, PF2B, PF3B and PF4B
(B) Amides PF5A, PF6A, PF7A and PF8A

2.2. Molecular docking

The crystal structure of the COVID-19 main protease (6LU7) was retrieved from the protein data bank (www.rcsb.org). The protease 6LU7 (resolution 2.16 Å) is a homodimer comprising two chains A and C with co-crystallized ligand, n-[(5-methylisoxazol-3-yl) carbonyl]alanyl-l-valyl-n~1~-((1r,2z)-4-(benzyloxy)-4-oxo-1-{[(3r)-2-oxopyrrolidin-3-yl]methyl}but-2-enyl)-l leucinamide. The structure of the compounds was prepared in .mol2 format using Chem 3D Pro and was optimized with MMFF94 Force Field using Avogadro 1.2.9 (Hanwell et al., 2014). These optimized compounds were docked with 6LU7 using two docking softwares for comparison: namely iGEMDOCK (Hsu et al., 2011) and LeDock (Zhao, 2017).

iGEMDOCK is a protein-ligand software which employs the application of a sophisticated biologically driven computational technique. It predicts the binding to the protein target of different molecules as well as evaluating the scoring function from the generated poses. The application of iGEMDOCK to several protein systems has shown that it has an accuracy that is comparable to other docking softwares. LeDock is a docking software that relies on the amalgamation of simulated annealing and evolutionary optimization of the position of the ligand, orientation as well as the rotatable bonds utilizing a scoring scheme based on the knowledge of physics which originated from prospective virtual screening campaigns (Zhao, Huang, 2011). The results were visualized using Discovery Studio 4.5 (BIOvIA, 2015) and PyMOL version 1.7.5.0 in order to understand the protein-ligand interactions. The docking procedure included the followings: binding site preparation, ligand preparation, setting up the receptor's binding site, dock ligands, analysis of results in terms of fitness and score. The results are shown in (Table 1) below.

For iGEMDOCK, the fitness score in the binding site is given as the total energy of a predicted pose. This fitness score is the empirical scoring function given by the following expression (eq. 1),

$$F = v + H + E \quad \text{.....1}$$

F is Fitness score, v, represents van der Waals energy, H, is hydrogen bonding while, Elec. represents the electrostatic energy.

2.3. Drug-likeness

The ADME (Absorption, Distribution, Metabolism, Excretion) and toxicity properties of the compounds were predicted using SWISS ADME (http://www.swissadme.ch/) (Daina et al., 2016). The drug-like properties were evaluated on the basis of Lipinski's rule. Druglikeness is an essential concept in drug discovery and delivery. It deals with how drug like a substance is with respect to a lot of factors. A drug like molecule is expected to show certain kind of characteristics with respect to solubility, lipophilicity, bioavailability, molecular structure etc. The Lipinski's rule of five is a standard for assessing druglikeness, however, there are other criteria according to the Lipinski's rule and ADME parameters; molecules that could serve as good oral drug candidates must respect certain conditions which include: maximum five and ten, hydrogen bond donors and hydrogen

acceptors respectively, maximum molecular coefficient (MLog P) value less than 4.15, molecular mass less than 500 Daltons (Adejoro et al., 2017).

2.4. Docking

The docking scores of the compounds obtained from iGEMDOCK (Figure 4) and LeDock (Figure 5) when PF1B, PF2B, PF3B, PF4B (Schiff bases), PF5A, PF6A, PF7A and PF8A (Amides) were docked against 6LU7 are shown in Table 1.

Table 1. Molecular docking scores of the compounds against 6LU7

Compounds	Fitness score (IGEMDOCK)	Ranking	LeDock Score (ΔG)	Ranking
PF1B	-93.90	7	-6.91	7
PF2B	-87.28	8	-6.86	8
PF3B	-99.77	3	-7.43	4
PF4B	-100.48	2	-7.33	6
PF5A	-101.42	1	-7.83	2
PF6A	-94.38	6	-7.94	1
PF7A	-96.46	4	-7.46	3
PF8A	-94.70	5	-7.36	5
chloroquine	-79.77		-5.23	
Favipiravir	-60.03		-5.63	
Co-crystallized ligand	-95.57		-5.38	

The hybrid compounds (Schiff bases and amides) had better docking scores than the chosen standards i.e. chloroquine and favipiravir. The high binding affinity may be as a result of the fusion of both drug candidates. The order of the compounds with respect to their docking scores suggests that the amide based compounds (PF5A, PF6A, PF7A, PF8A) are better potential inhibitors than the Schiff bases PF1B, PF2B, PF3B, PF4B. This might be due to the presence of the carbonyl group as it is known to account for increased interaction in biomolecules via hydrogen bonding. The compounds containing the hydroxyl and fluorine groups also had better docking scores than the others. This is due to enhanced interaction between the protein and the ligand especially with respect to hydrogen bonding. The trend for the docking scores with respect to LeDock is: PF6A > PF5A > PF7A > PF3B > PF8A > PF4B > PF1B > PF2B. The fitness scores result from IGEMDOCK showed a similar trend: PF5A > PF4B > PF3B > PF7A > PF8A > PF6A > PF1B > PF2B. All the compounds had better docking scores in comparison with the standards chloroquine and favipiravir. Figures 4 and 5, show the graphical display of the docking scores between 6LU7 and PF compounds using IGEMDOCK and LeDock respectively (The binding energy is shown in minus kcal/mol, while the fitness scores is negative).

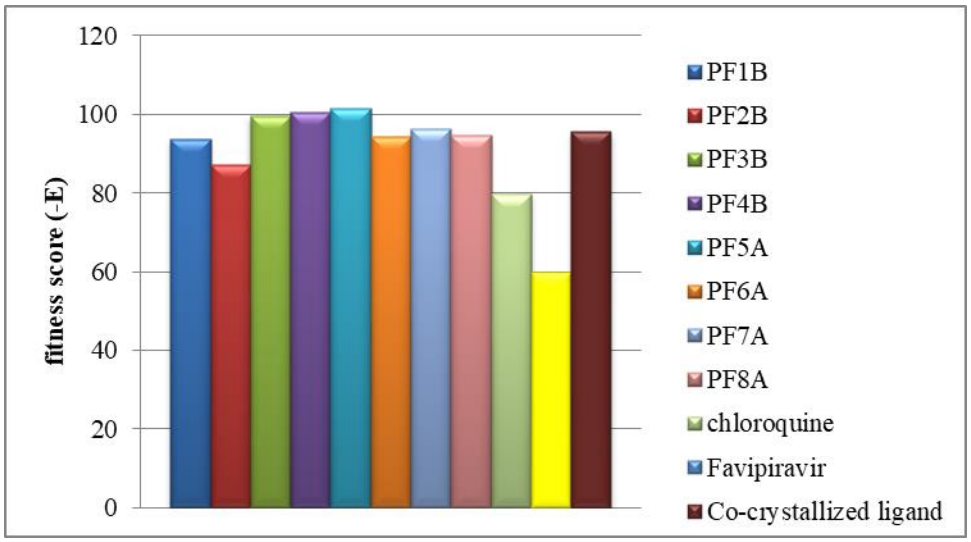


Fig. 4. Molecular docking results between 6LU7 and primaquine-favipiravir compounds using iGEMDOCK

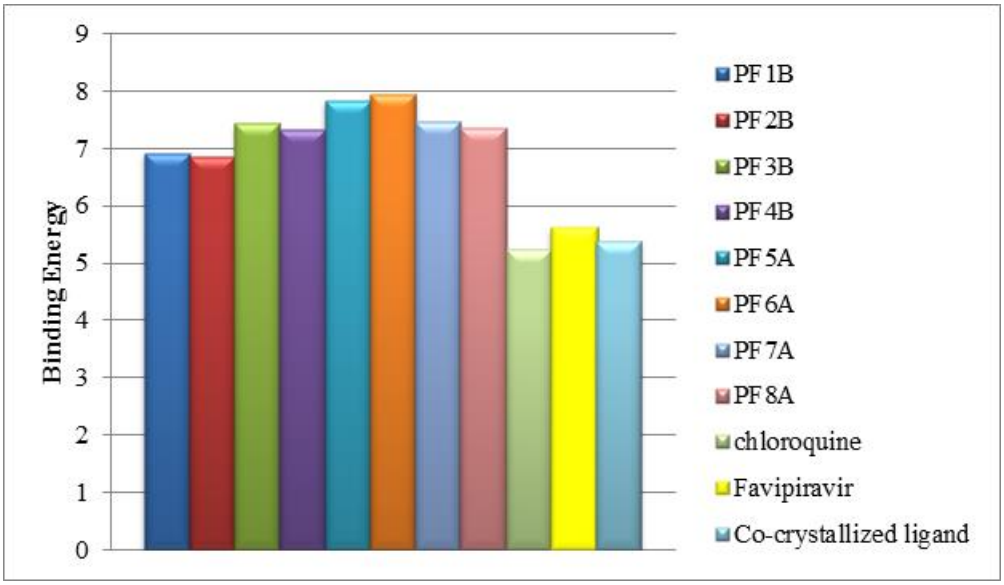


Fig. 5. Molecular docking results between 6LU7 and primaquine-favipiravir compounds using LeDock

The protein structure of 6LU7 and its co-crystallized ligand is presented (Figure 6), which reveals PHE140, LEU 141, HIS 172, HIS 164, HIS 163, LEU 167, GLY 143, HIS 41, MET 49, GLN 189, THR 190, PRO 168, ALA 191, LEU 167, GLU 166, GLU 164, HIS 164, MET 165, GLY 143 as common amino acids that interacts with the co-crystallized ligand. The mode of binding of these compounds to the target protein are shown (Figure 7a-j). The compounds interact with similar amino acids contained in the A strand of the protease protein 6LU7. Favipiravir and chloroquine both promising drugs for the treatment of the coronavirus disease interacted with PRO 168 and GLU 166. PF1B interacts with LEU 167 via an amide pi-stacked interaction and with GLU 166 and MET 165 through a carbon-hydrogen bond, it also interacts with PRO 168 via a pi-alkyl mode. PF2B and PF5A interact with just two of the amino acid; PRO 168 and ALA 191 through pi-alkyl interactions and pi-sigma bond. Others are through van der Waals interaction. PF6A interacted with PRO 168, THR 190, ALA 191, LEU 167 through pi-alkyl and amide-pi stacked interactions. PF3B and PF4B showed hydrogen bonds with ALA 191, GLY 170 the other interactions were with PRO 168 and GLU 166 via Halogen and carbon-hydrogen bond respectively. PF7A interacts with GLY 170, PRO 168, and GLU 166 via the halogen (Fluorine) other amino acids like THR 190 and

ALA 191 interacted with ligand in other ways. PF8A interacted with the protein via several amino acids namely PRO 168 through a pie-lone pair, 168, ALA 191, GLU 166 through a hydrogen bond. All these interactions account for the docking scores predicted for each ligand as the affinity of drug compounds to proteins is dependent on the type and amount of bonding that exists between the drug and protein target. The 2D diagram showing interaction between the compounds and the protein (6LU7) is shown (Figure 7). PyMOL was used to visualize the compounds in the cavity of the protein (Figure 8).

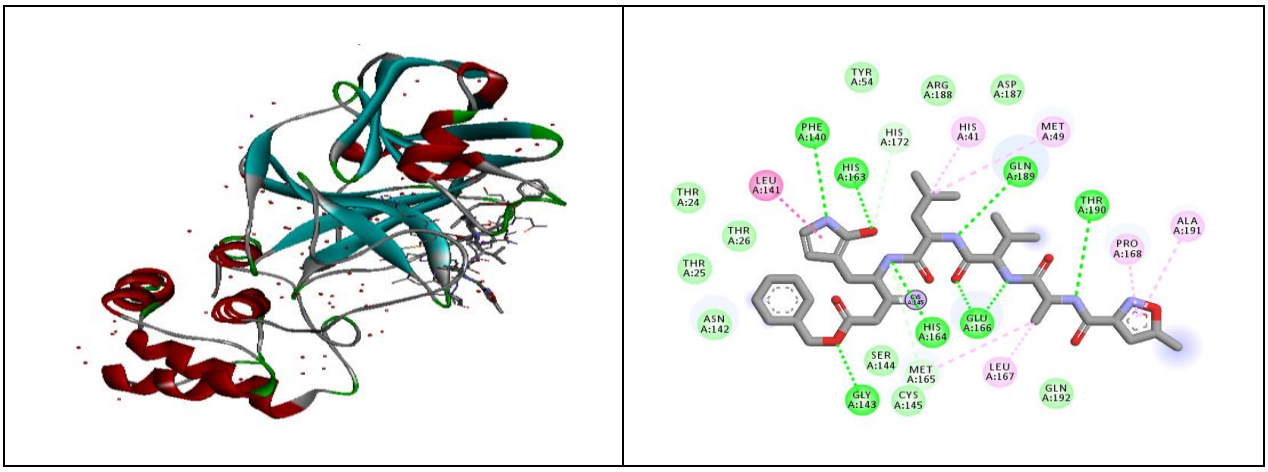
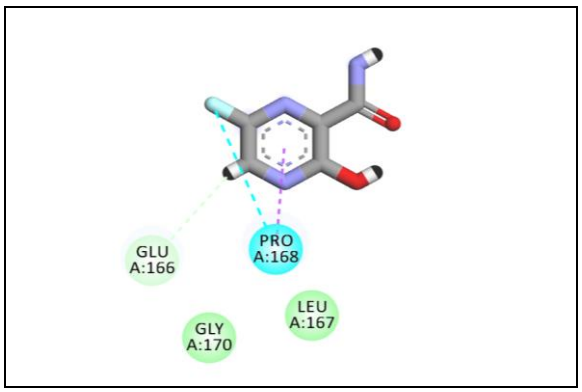
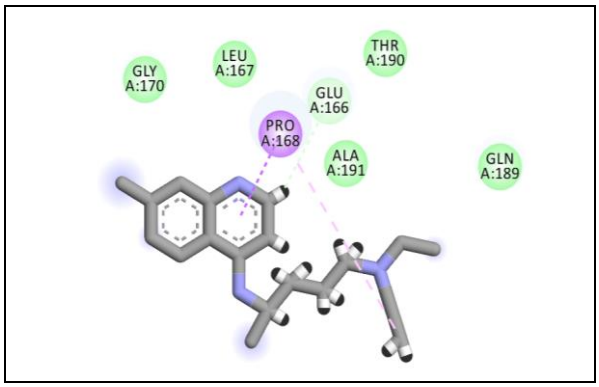


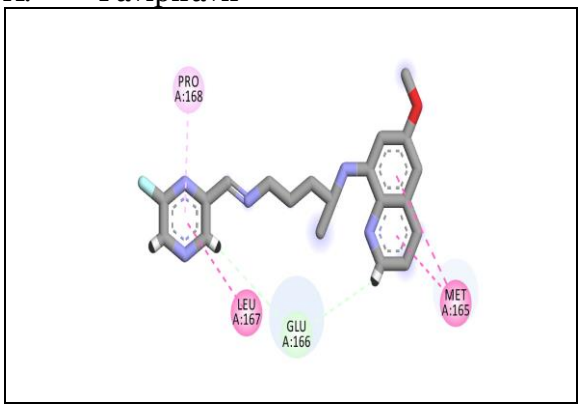
Fig. 6. The protein 6LU7 and its co-crystallized ligand



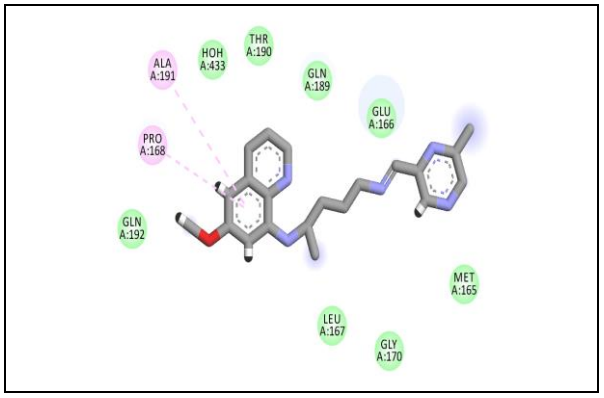
A. Favipiravir



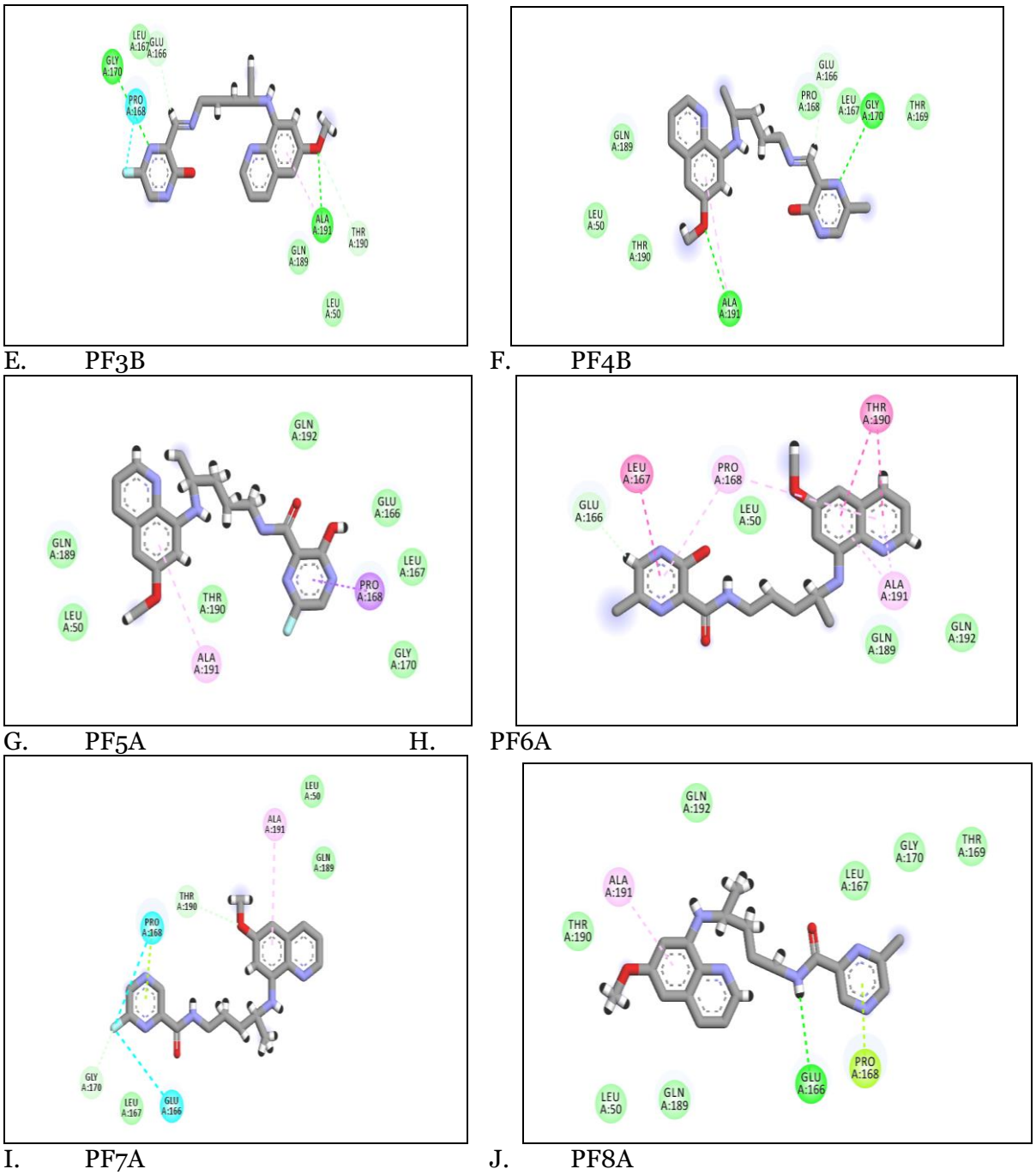
B. Chloroquine



C. PF1B



D. PF2B



E. PF3B F. PF4B

G. PF5A H. PF6A

I. PF7A J. PF8A

Fig. 7. 2D Diagram showing Interaction between virus main protease (6LU7), chloroquine, favipiravir and the potential inhibitor candidates

(A) Chloroquine

(B) Favipiravir

(C) (Z)-5-fluoro-3-(((4-((6-methoxyquinolin-8-yl)amino)pentyl)imino)methyl)pyrazin-2-ol Schiff bases derivatives (PF1B, PF2B, PF3B and PF4B)

(D) 6-fluoro-3-hydroxy-N-(4-((6-methoxyquinolin-8-yl)amino)pentyl)pyrazine-2-carboxamide derivatives (PF5A, PF6A, PF7A and PF8A)

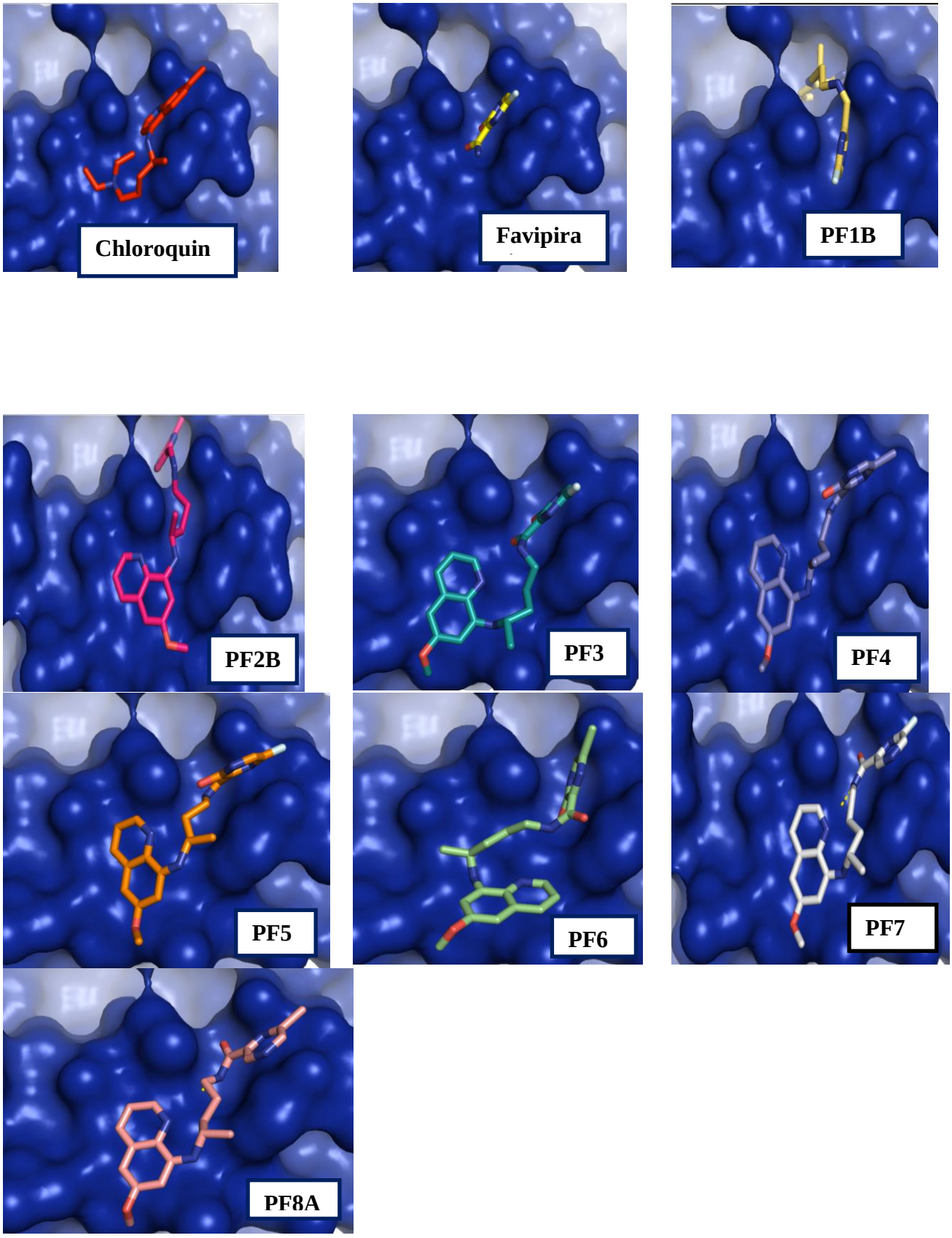


Fig. 8. Molecular docking visualization of chloroquine, favipiravir, PF1B, PF2B, PF3B, PF4B, PF5A, PF6A, PF7A and PF8A in 6LU7 using PyMOL

2.5. Druglikeness

The ADME results obtained revealed that all the compounds analyzed (PFB and PFA) qualify as drug candidates as they satisfy the conditions for oral drug candidates (Table 2).

Table 2. Druglikeness parameters for Schiff bases (PFB) and Amides (PFA)

Compounds	Formula	MW	H-bond acceptors	H-bond donors	MLOGP	Lipinski violations
PF1B	$C_{20}H_{22}FN_5O$	383.42	7	2	0.88	0
PF2B	$C_{20}H_{22}ClN_5O_2$	399.87	6	2	0.99	0
PF3B	$C_{20}H_{22}FN_5O$	367.42	6	1	1.01	0
PF4B	$C_{20}H_{22}ClN_5O$	383.87	5	1	1.12	0
PF5A	$C_{20}H_{22}ClN_5O_3$	399.42	7	3	0.77	0
PF6A	$C_{20}H_{22}ClN_5O_3$	415.87	6	3	0.88	0
PF7A	$C_{20}H_{22}FN_5O_2$	383.42	6	2	0.88	0
PF8A	$C_{20}H_{22}ClN_5O_2$	399.87	5	2	0.99	0
Chloroquine	$C_{18}H_{26}ClN_3$	319.87	2	1	3.20	0
Favipiravir	$C_5H_4FN_3O_2$	157.10	5	2	-1.36	0

3. Conclusion

The theoretical evaluation of the Schiff bases and amides obtained from the fusion of primaquine and favipiravir exhibited better interaction with the protease derived from the coronavirus. They also gave better docking scores than the frontline drugs in the treatment of coronavirus disease, i.e. chloroquine and Favipiravir. The druglikeness studies of the proposed compounds also showed that they all qualify as potential oral drugs as they satisfy the Lipinski's rule. Thus, they could qualify as potential drug for the treatment of COVID-19, subject to confirmatory procedures for pre-clinical and clinical investigations.

4. Conflict of interest

We wish to confirm that there are no conflicts of interest associated with this publication, has not been published before and not currently being considered for publication elsewhere.

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