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In silico ADME, Bioactivity and Toxicity Prediction of some Selected Antiviral Drugs

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ABSTRACT

Viruses have been the cause of some of the world's worst and most dreadful diseases. COVID-19 is one of them, and it is the name given to the novel corona virus discovered in 2019. Due to the unavailability of any proven treatment, there is an urgent need for therapeutics for COVID-19. In this computational investigation, ADME profiles and bioactivity results of 2-deoxy D-glucose (**1**), Hydroxy chloroquine (**2**), and Favipiravir (**3**) compounds were calculated. Drug likeness criteria based on Lipinski and Veber's rules indicate that the compounds have classic physicochemical and pharmacokinetic properties that make them a good candidate for oral drug administration.

Keywords: Insilco, Antiviral, Drug likeness, ADME, COVID-19.

I. INTRODUCTION

Viruses are major pathogenic agents causing various severe diseases in humans, other animals, and plants. As one of the most pervasive forms of life, viruses may infect every type of animal, from mammals to insects, plants, and even microorganisms. The earth appears to have more virus species than all other animal species combined.

The WHO designated the corona virus disease of 2019 as COVID-19 in February 2020 [1]. Formerly, six corona viruses were recognized to cause diseases in humans, and these could be defined as low or highly pathogenic Coves [2]. According to the World Health Organization, the WHO China Office reported pneumonia of unknown etiology in Wuhan City at the end of 2019 [3]. The Chinese authority on health showed that the patients primarily tested negatively for viruses and respiratory bacteria but later tested positive for a new corona virus. Chinese scientists immediately isolated the virus and sequenced its genome.

COVID-19 can cause infections in different animals and most infections of the respiratory tract in individuals, including Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). The COVID-19 virus is completely different from the viruses responsible for SARS and

MERS [4]. The COVID-19 genome sequences obtained from the patient's body are 79.5% identical to SARS-Cove. The signs and symptoms characteristically occur within two weeks after contact and consist of fever, coughing, respiratory disorders, pain in the chest, and trouble breathing. Possibly deadly complications include pneumonia and kidney failure [5]. In the current state of affairs, the United States of America and most European countries bear the lion's share of the burden of illness and death associated with COVID-19 when compared to other countries. The latest increase in consistently reported patients with COVID-19 has now reached acute care stocks, restricting acute care coverage to just a limited percentage of critical patients. This may also have led to the elevated fatality ratio found during the COVID-19 outbreak.

In abundant recent works, 2-deoxy D-glucose, Hydroxychloroquine, and Favipiravir have been designed for experimental treatments of COVID-19, which has been recommended as a helpful drug for the purpose [6]. Computer-aided drug design (CADD) has recently been utilized successfully in drug discovery.

.On May 8, 2021, the Drugs Controller General of India approved an oral formulation of 2-deoxy-D-glucose for emergency use as an adjunct therapy in moderate to severe corona virus patients. The medication was created by the DRDO and Dr. Reddy's Laboratories. In a news statement, the two organizations stated that the medication "helps in speedier recovery of hospitalized patients and lowers supplementary oxygen dependence [7].

2-deoxy D-glucose (**Fig. 1**) has been used as a targeted optical imaging agent for fluorescent *in vivo* imaging. In clinical medical imaging (PET scanning), Fluorodeoxyglucose is used, where one of the 2-hydrogens of 2-deoxy-D-glucose is replaced with the positron-emitting isotope Fluorin-18 which pairs Gamma rays, allowing the distribution of the tracer to be imaged by an external gamma camera. This is increasingly done in tandem with a CT function that is part of the same PET/CT machine, to allow better localization of small-volume tissue glucose-uptake differences.

Hydroxychloroquine (**Fig. 1**) is a quinoline medicine used to treat or prevent malaria a disease caused by parasites that enter the body through the bite of a mosquito. Africa, South America, and Southern Asia are among the regions where malaria is prevalent. All strains of malaria or malaria in regions where the infection has proven resistant to a treatment similar to chloroquine are not treatable by hydroxychloroquine. Additionally, discoid or systemic lupus erythematosus and rheumatoid arthritis symptoms are managed with hydroxychloroquine.

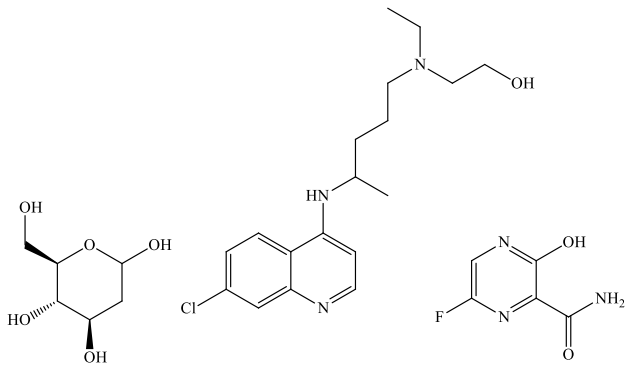
Favipiravir (**Fig. 1**) is an antiviral medication with a pyrazine structure that was developed by the Fujifilm group in Japan and has an action against a wide range of RNA viruses [8]. It has been more thoroughly examined for different types of influenza in the last few years. In abundant recent works, Favipiravir has been designed for experimental treatments of COVID-19, in which it has been recommended as a helpful drug for the purpose.

In this research investigation, we performed a computational evaluation of ADME, bioactivity, and toxicity parameters of some selected anti-viral agents.

II. METHODS AND MATERIAL

Computer-aided drug design (CADD) has recently been utilized successfully in drug discovery. This method requires substantially less effort, time, and money when compared to traditional approaches. The use of computational technology for identifying the new candidate drugs help to reduce the number of experimental studies and for improving the success rate. For this reason, we used the ADMET

(adsorption, distribution, metabolism, excretion and toxicity) profile for a measure of the pharmacokinetics parameters of the three compounds proposed by the Pre-ADMET server, to evaluate their chances to become a candidate drug in the future.



2-deoxy D-Glucose (1) **Hydroxy Chloroquin (2)** **Favipiravir (3)**

Fig 1. Structures of 2-deoxy D-Glucose, Hydroxy chloroquin, and Favipiravir.

Computational techniques were applied to analyze the various physiochemical features of Pharmacokinetic descriptors which were calculated for the **1-3** compounds through the online tool Molinspiration Cheminformatics server [9] (http://molinspiration.com/). ADMET SAR2 [10] was used to predict the absorption, distribution, metabolism, and toxicity properties of the selected compounds. The parameters of the compounds' oral bioavailability were examined using the SwissADME website.

III. RESULTS AND DISCUSSION

The word "drug similarity" refers to the superior concept of a property that is comparable to a recognized drug and is defined as a complicated equilibrium of several molecular properties and structural traits. These molecular characteristics include, among others, bioavailability, transport properties, interactions with proteins, reactivity, toxicity, metabolic stability, and many others. The main ones are hydrophobicity, electronic distribution, hydrogen bonding properties, and the existence of various pharmacological characteristics that affect how molecules are used by organisms. Lipinski's rule of five was used to determine the bioavailability of bulk materials to examine the drug-likeness properties. This rule is crucial for the development of new drugs. In the present study, the physiochemical properties analysis of molecules was carried out with the Molinspiration Cheminformatics program, and drug-likeness of the **1-3** molecules was calculated and it is presented in **Table 1**. The study of good membrane permeability of molecules should obey the following: H-bond donors (HBD) were found in-between 1-3 (≤5), H-bond acceptors (HBA Å ^{2}) were found to be 3-5 (≤10), all **1-3** molecules partition coefficient (Mi log P) is less (≤5), molecular weight is also less than (≤500g/mol), Vander Walls topological polar surface area (TPSA) value is 48.38-90.15Å ^{2} (≤120 Å^2). So, the compounds obey Lipinski's rule of five for all cases.

Table 1. Drug likeness prediction of **1-3** compounds using molinspiration online tool.

Compound:	**1**	**2**	**3**
Molecular formula:	$C_6H_{12}O_5$	$C_{18}H_{26}ClN_3O$	$C_5H_4FN_3O_2$
Molecular weight(g/mol):	164.16	321.85	157.10
mi log P:	-1.95	3.98	-0.52
TPSA(Å²)	90.15	48.38	89.11
No. of H bond acceptor:	2	4	5
No. of H bond donor:	1	2	3
No. of rotatable bonds:	1	8	1
No. of violations	0	0	0
Rule of five violations	0	0	0

Topological polar surface area (TPSA).

The bioactivity score of compounds **1-3**, Ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor values are given in **Table 2.**

Table 2. Bioactivity score of 1-3 compounds.

Parameter	1		2	3
Bioactivity	**GPCR Ligand**	-0.52	0.31	-0.43
	ICM	-0.13	0.16	0.42
	KI	-0.84	0.33	-0.35
	NRL	-0.78	-0.23	-1.14
	PI	-0.34	0.04	-0.58
	EI	0.69	0.00	-0.18

GPCRL: G protein-coupled receptor ligand;
ICM: Ion channel modulator;
KI: Kinase inhibitor;
NRL: Nuclear receptor ligand;
PI: Protease inhibitor;
EI: Enzyme inhibitor.

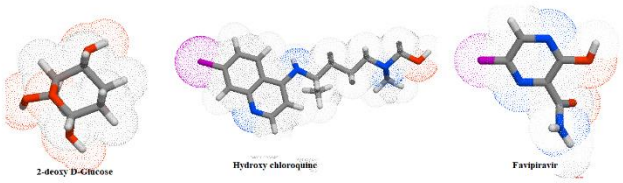


Fig 2: Stable conformations of compounds 2-deoxy D-Glucose (**1**), Hydroxy chloroquine (**2**), and Favipiravir **(3).**

Table 3. ADMET prediction of 1-3 compounds.

Properties	Compound 1	Compound 2	Compound 3
AlogP98	-1.747100	3.457400	-0.182000
Surface area	63.849	136.659	60.697
Adsorption			
Pure water solubility (mg/L)	930297	224.786	13724.8
Buffer solubility (mg/L)	283303	12.9119	195.055
Caco-2 permeability	7.70057	46.0839	17.0145
P_{gp} inhibition	Non	Non	Non
Skin permeability	-4.98488	-3.08546	-4.43154
Human-Intestinal adsorption (%)	62.522	88.049	100
Distribution			
BBB permeability(log BB)	0.0987037	2.28794	0.25861
VDss (human, log L/kg)	-0.232	1.021	-0.262
CNS permeability	-3.6	-2.654	-3.037
Fraction unbound	0.898	0.286	0.737
Metabolism			
CYP 2C19 inhibition	Inhibitor	Non	Inhibitor
CYP 2C9 inhibition	Inhibitor	Non	Inhibitor
CYP 2D6 inhibition	Non	Inhibitor	Non
CYP 2D6 substrate	Non	Substrate	Non
CYP 3A4 substrate	Weakly	Weakly	Non
CYP 3A4 inhibition	Non	Non	Non
HIA	41.652679	94.660945	72.7553
MDCK	0.583686	45.1085	1.66307
Plasma protein binding	42.018589	88.996812	3.519089
SKlogD-value	-1.784380	2.058490	-0.75472
SklogP-value	-1.784380	3.622950	-0.75472
SklogS-buffer	0.236990	-4.415190	-2.90603
SklogS-pure	0.753360	3.174410	-1.05868
Excretion			
Total clearance (log ml/min/kg)	0.611	1.096	0.861
Renal OCT2 substrate	No	No	No
Toxicity			

Algae at	0.195245	0.0108916	0.233301
Ames test	mutagen	mutagen	mutagen
Carcino-Mouse	negative	negative	negative
Carcino-Rat	negative	negative	positive
Daphnia-rat	15.7025	0.0554527	1.66438
hERG-inhibition	low risk	medium risk	low risk
Medaka-at	210.661	0.00582202	3.15729
Minnow -at	93.6604	0.00995439	1.2034
TA100 -10RLI	negative	negative	negative
TA100 -NA	positive	negative	positive
TA1535-10RLI	negative	negative	positive
TA1535-NA	negative	negative	positive

MW (molecular weight (g/mol));
log P (partition coefficient);
colon cancer cell line (Caco-2);
N_{rot} (number of rotatable bonds);
Fsp3 (fraction Csp3);
N_{vio}(number of violations by the Lipinski and Veberdruglikeness criteria);
HIA (human intestinal absorption);
Caco-2 (human adenocarcinoma colon cells) ;
BBB (blood-brain barrier penetration);
Pgp (Pglycoprotein substrate);
GPCR (G-protein coupled receptor);
ICM (ion channel modulator);
Kinase inhibitor;
Nuclear receptor ligand;
Protease inhibitor;
Enzyme inhibitor models;
Toxicity by the acute oral model.

The Swiss ADME web tool was used to determine the oral bioavailability and other physicochemical characteristics of the chosen substances and standards. The bioavailability radar (**Fig. 3**) gives a swift catch sight of the important physicochemical properties and drug-likeness of the selected compounds. As shown in (**Fig. 3**), the colour portion (Pink) shows the most desirable area for each of the bioavailability properties (LIPO, SIZE, INSOLU, POLAR, INSATU, and FLEX). Surprisingly, all the selected compounds and standards were in the coloue region. According to Lipinski rule of five (RO5), the SIZE (Molecular Weight) of a good drug candidate is expected not to be more than 500 gmol-1, of which of all selected compounds (**1-3**). The INSOLU (insolubility) requirement of the selected compounds and standards as depicted in their ESOL (Log S) and ESOL Class revealed that compounds **1-3** are very soluble. All the selected compounds fall within the INSATU recommended range of values and have the best oral bioavailability since all their physicochemical properties fall within the optimal colour (pink) region.

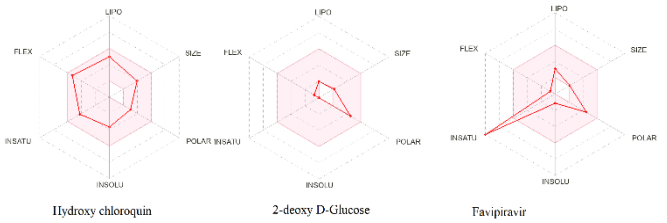


Fig.3: The bioavailability radar for the selected compounds.
Pink area = Most desirable area for each of the bioavailability properties;
LIPO = Lipophilicity;
POLAR = Polarity;
INSOLU = Insolubility;
FLEX = Flexibility;
SIZE = Molecular weight;
INSATU = Unsaturation.

In silico ADMET (absorption, distribution, metabolism, excretion, and toxicity) screening of drugs could avoid the tremendous cost and time associated with the in vivo experiments, and attract more and more attention. As shown in ADMET properties in **Table 3**, three compounds exhibited positive results for blood-brain barrier (BBB) criteria i.e. they can pass through BBB, possess good human intestinal absorption value, and Hydroxy chloroquine shows high BBB value. All the **1-3** compounds are non-carcinogenic and showed a safer category of acute oral toxicity. So, they are relatively harmless and safe for oral administration. The three compounds

showed inhibition to the P-glycoprotein inhibitor where, the inhibition can interrupt the absorption, permeability, and retention of the compounds. Inhibition of the potassium channels by the human ether-a-go-related gene (hERG) mainly generates QT syndrome-leading to fatal ventricular arrhythmia [10], and the need to withdraw many drugs from pharmaceutical market. In the present study, three the compounds showed weak inhibitory features towards human hERG and hence comparatively safer. For metabolism, all compounds were predicted to be No Inhibitor for the CYP450 3A4, which meant that they might be metabolized by CYP 3A4. In addition, all compounds might not inhibit CYP450 1A2 isoform, but they might inhibit CYP450 3A4 isoform. Based on the predicted total clearance rate, liver and kidney tissue could be used to clear all compounds in combination. The expected toxicity indicated that all compounds might be harmful to the liver and that none of them caused skin irritation and mutagenicity. All design molecules with synthetic accessibility scores showed lower structural complexity, thus demonstrating synthetic feasibility (**Table 3**). Computational pharmacokinetic and toxicological studies and accessible synthetic methods indicated that virtually designed compounds could be used as lead compounds for further development. Overall the ADMET results ensure good drug-likeliness properties and hence could be a potent new possible candidate for better performance.

IV. CONCLUSION

Scientists are working hard to determine the new corona virus's characterization and develop antivirus therapies and vaccines. However, the virus's pathogenesis is still not fully known, and new studies are needed in this regard. Currently, the only way to prevent the spread of Covid-19 is an effective infection control method. The most appropriate treatment for patients under observation diagnosed with Covid-19 is still unknown. Therefore, treatment protocols should be followed within the framework of existing health rules some vaccines have been developed, and the prophylactic drug has not yet been developed, although intensive trials are ongoing for both. Although some vaccines have been developed for the COVID-19 corona virus, intensive work is still being done to develop specific drugs or vaccines. Computational pharmacokinetic and toxicological studies and accessible synthetic methods indicated these **1-3** compounds could be used as lead compounds. Overall the ADMET results ensure good drug-likeliness properties and hence could be potent new possible candidates for better performance.

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