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FDA recommended potent drugs against COVID-19: Insight through molecular docking

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ABSTRACT

Human Coronavirus (COVID-19) is a worldwide pandemic of 2019–20 that was emerged in China in December 2019. More than 37,000deaths with7, 84, 440confirmed cases has been reported from around 200 different countries has been reported till now and the number is increasing every second. The spread is said to be through human to human transmission via close contact or respiratory droplets produced when people cough or sneeze. No treatment for the illness has been approved yet. The urgent need is to find solution to this growing problem that has affected the whole mankind. World Health Organisation (WHO) as well as US Food and Drug Administration (FDA) are continuously working to find the solution. In the same line they have proposed many potent drugs that may have efficiency against the newly emerged viral infection. To support the efforts the present study is designed to carry out the *in silico* analysis *viz.* Docking studies of around 16drugs recently recommended by US FDA by observing the interaction of test molecules with SARS proteinase.

Selection and peer-review under responsibility of the scientific committee of the International Conference on Advances in Materials Research – 2019.

1. Introduction

COVID-19 is a newlyarisen human coronavirus, testified in Wuhan, China inDecember 2019 [1,2]. The severity of the disease was earlier found only in China but now became uncontrollable problem all over the world. On January 30, 2020, it is statedasPublic Health Emergency of International Concernby WHO and later on 11 March 2020 it was declared a pandemic.It is originated from seafood market and leading to viral pneumonia leading to the emergence of the outbreak [3]. The number of cases aregrossly increasing daily, with confirmed cases exceeding7, 84, 440 confirmed cases with greater than 37,000 deaths in around 200 different countries.A single stranded RNA virus ofCoronaviridae family is considered to be thecause of this severe acute respiratory syndrome [4–7]. The terrible manifestations of this infection include fever, cough,and breath failure allied with respiratoryproblem. High pervasiveness of hospitalization and with mortalityrisk of more than 15%, and lack of prophylacticvaccines and therapeutic conventions, embrace serioustasks of SARS at time of worldwide outbreaks [8–11]. TheSARS genome encodes 2 polyproteins thatare cleaved to dissimilar functionalproteins of envelop, spike,nucleo protein,polymerase, replicase, and membrane[12–14].

WHO is putting huge efforts in finding specific treatments with many under clinical trialsbefore reaching the final solution.In scientific world, the race is on to find a drug that might help save severely ill patients.But obviously even with rapid government approval, it could take months to develop new drugs from scratch that might be effective against the virus.Thus computer modelling studies on certain drugs already approved by the U.S. Food and Drug Administration, to assess their potential in combating the coronavirus is something that can be done at present.Several antiviral drugs such as Darunavir, Nelfinavir, and Saquinavir; the ACE inhibitor Moexipril; the chemotherapy drugs Daunorubicin and Mitoxantrone; cholesterol-lowering statin rosuvastatin;the painkiller Metamizole; the antihistamine Bepotastine; and the antimalarial drug Atovaquone, Chlorquinone and hydroxychloroquine are some of the drugs under scrutiny [15]. The present study is aimed to further support the potency of these test molecules on the basis of their interaction withSARS proteinase through docking experimentto comprehend the mechanismsused forscheming-morepromising drugs against SARSinfection.

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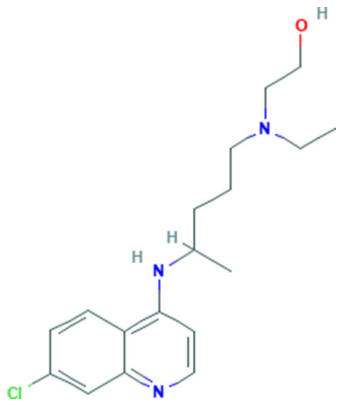
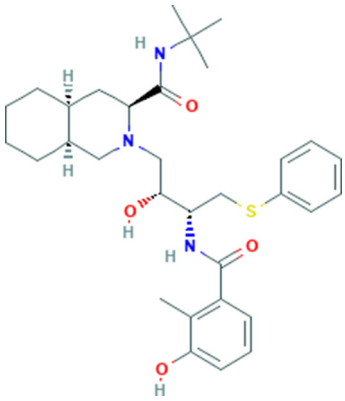
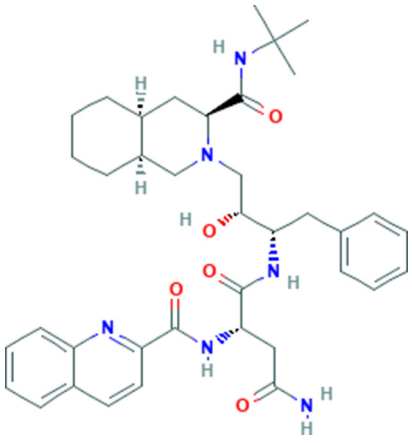
Table 1
Structural analysis and Binding energy of test drugs.

Molecule	*Structure*	*Binding Energy (Kcal/mol)*
Darunavir (I)		*−10.2*
Nelfinavir (II)		*−11.1*
Saquinavir (III)		*−11.5*
Ritonavir (IV)		*−9.8*

(*continued on next page*)

Table 1 (*continued*)

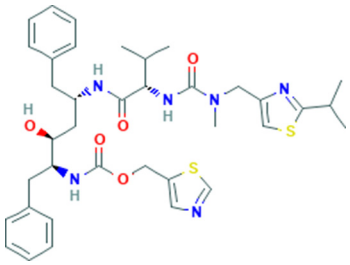
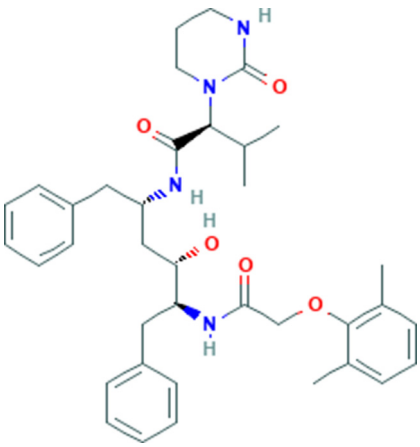
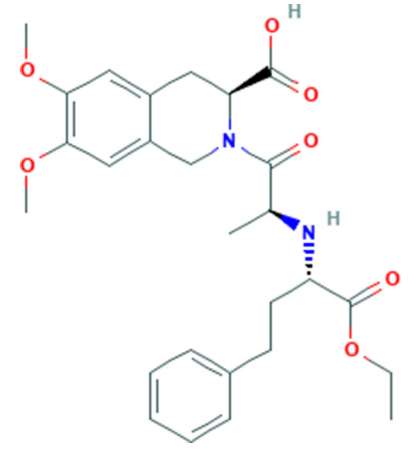
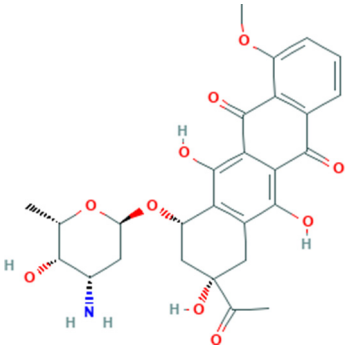
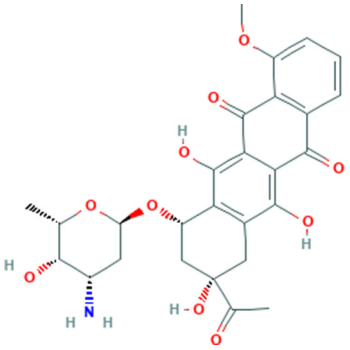
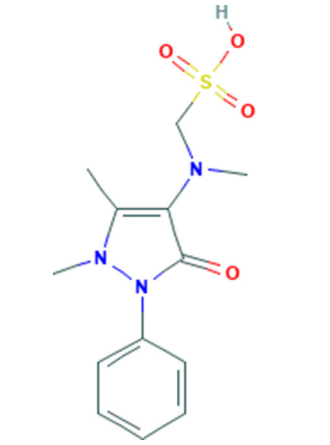
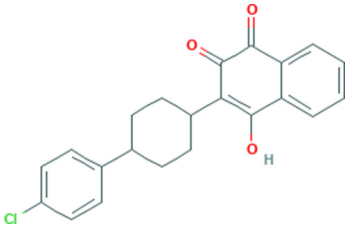
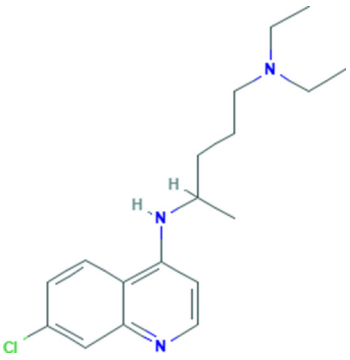
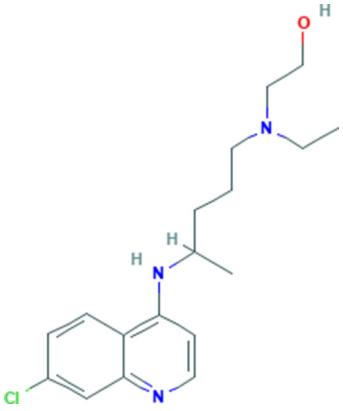
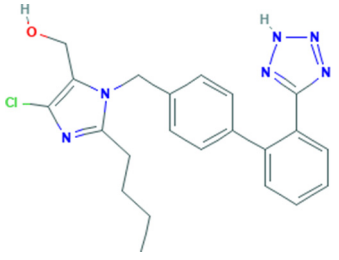
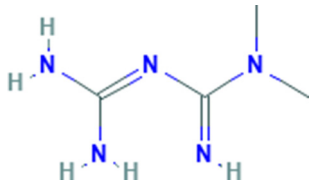
Molecule	*Structure*	*Binding Energy (Kcal/mol)*
Liponavir (V)		*−9.7*
Moexipril (VI)		*−8.7*
Daunorubicin (VII)		*−10.7*
Rosuvastatin (VIII)		*−8.5*

Table 1 (*continued*)

Molecule	*Structure*	*Binding Energy (Kcal/mol)*
Metamizole (IX)		*−7.6*
Atovquinone (X)		*−9.5*
Chlorquine (XI)		*−7.0*
Hydroxychloroquine (XII)		*−6.8*

(*continued on next page*)

Table 1 (*continued*)

Molecule	*Structure*	*Binding Energy (Kcal/mol)*
Losartan (XIII)		*−7.4*
Metformin (XIV)		*−4.0*
Haloperidol (XV)		*−8.5*

2. Experimentation

2.1. Docking studies

Docking strategy was utilized to find the binding efficiency of test molecules in active site of SARS-CoV main protease, using AutoDockTools-1.5.6 software. Enzyme comprises the crystal structureof Mpro(PDBID: 1UK3)[16]. It is acquired by the X-Raydiffraction technique and developed at the resolutions of 2.4 Å [17]. The enzymes were made to bind with compound and docking score was calculated. The more negative energy represents the effective binding and hence activity of compound.

2.2. Ligand retrieval

Sixteen different FDA recommended drugs were considered for the study: antiviral drugs such as Darunavir (I), Nelfinavir (II), and Saquinavir (III); HIV drugs Ritonavir (IV), and Lopinavir (V); the ACE inhibitor Moexipril (VI); the chemotherapy drugs Daunorubicin (VII); cholesterol-lowering statin rosuvastatin (VIII); the painkiller Metamizole (IX); and the antimalarial drug Atovaquone (X), Chlorquinone(XI) and hydroxychloroquine (XII); blood pressure drug Losartan (XIII); antibiotic Metformin (XIV); Schizophrenia drug haloperidol (XV); against Ebola Remdesivir (XVI). The compounds were preparedwith help of PubChem database and

the 3D structure of the ligands wereregainedin SDF format from PubChem Compound database followed by conversion in the PDB format and optimization using Marvin Sketch. Molecular mechanics were utilized to createtherepresentative geometry for the majority of test moietiesdue to the fact of being extremely parameterized. The pdb-files were converted to PDBQT by using AutoDockTools-1.5.6 [18,19].

2.3. Preparation of active site

The active binding site was found from the selected protein by CASTp2.0 server [20].

2.4. Preparation of protein

The protein was saved as pdb-file and the attached water molecules were deleted and polar hydrogens were added in AutoDockTools-1.5.6and then saved as PDBQT. Before dstarting the next procedure, docking grid box was set with centrex = 82.665, centrey = -15.887, centrez = 31.008 of sizex = 70, sizey = 40, sizez = 56.AutodockVina was used to carry out docking and PyMol for virtual screening.

2.5. Ligand-protein interactions

Allouput files corresponding to 16 ligands were obtained from AutoDockVina were analysed by using PyMol. The interactions between docked molecule and protein can be seen via hydrogen bonding with different amino acid residues of protein and the given compound.Theindication of hydrogen bonds were signifiedby dashed lines between the atoms,while hydrophobic bonding are indicated by an arc with spokes radiating towards the atoms of ligands.

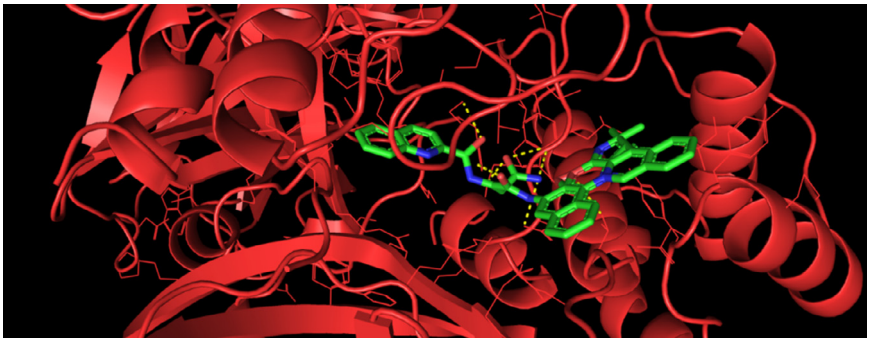


Fig. 1. Docked Saquinavir with protein showing three hydrogen bonds.

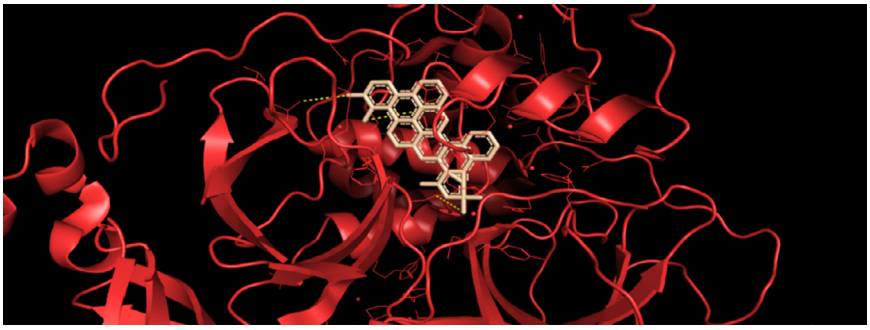


Fig. 2. Docked Nelfinavir Show interaction via three hydrogen bonds.

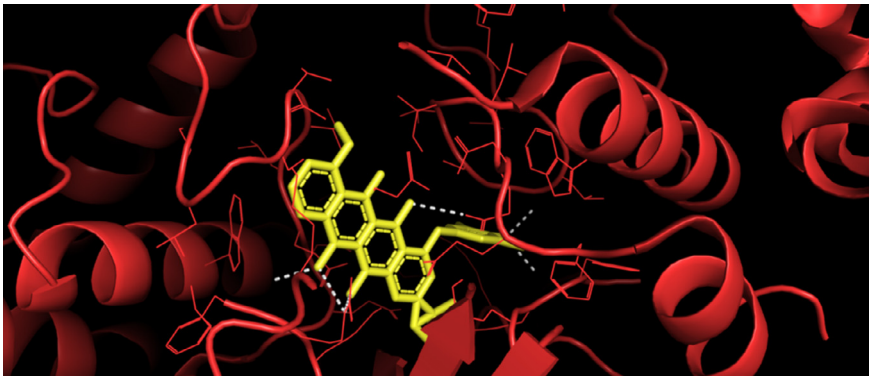


Fig. 3. Docked Daunorubicin Show interaction via two hydrogen bonds.

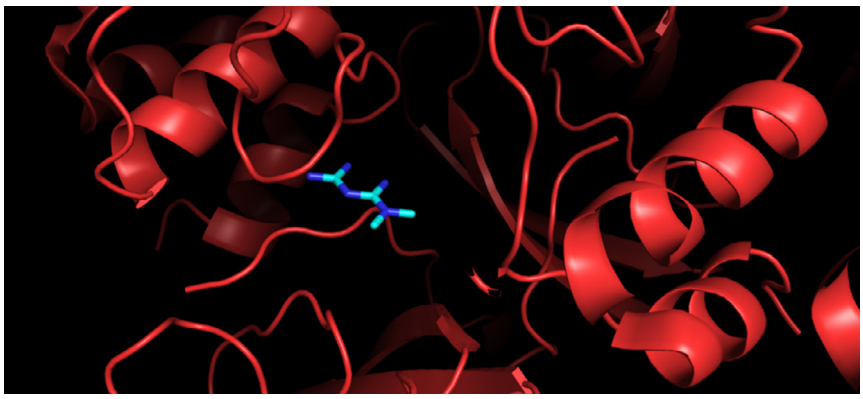


Fig. 4. Docked Metformin showed no interaction with enzyme.

3. Results and discussion

The selected molecules were investigated for their best co-inhibiting activities in the enzyme. Therefore, molecular docking of designed hybrids were carried out into the active site of the enymeSARS-CoV main protease(PDBID: 1UK3) using AutoDockTools-1.5.6.

All the test molecules fitted into the binding pocket of SARS-CoV main proteaseand showed appreciable docking score. Out of 16test drugs, 14 drugs showed docking scores $\geq$ -7.0 Kcal/mol. Best among them with docking score of more than −10.0 Kcal/mol that shows strong binding in the pocket of an enzyme are Saquinavir (-11.5 Kcal/mol) followed by Nelfinavir (-11.1 kcal/mol); Daunorubicin (-10.7 kcal/mol) and Darunavir (-10.2 Kcal/mol). The results with structural analysis are shown in Table 1

Binding modes of the selected compoundswere studied using Pymol. Hydrophobic interaction as well as hydrogen bonding results in the strong binding interactions. The prominent bonding in Saquinavir, Nelfinavir and Daunorubicindue to hydrogen bond interactions in the binding pockets of the target enzyme is shown in Figs. 1-3 and for sake of comparison absence of bonding interactions leading to poor binding energy of metformin is shown in Fig. 4.

Saquinavir form three hydrogen bond with three amino acid residues*i.e.* Glutamic acid (286),

aspartic acid(286)and third with serine (281). Nelfinavir also showed three hydrogen bond with active arginine (6), glutamic acid (286) and aspartic acid.On the other hand, Daunorubicinform only hydrogen bonding with arginine (6) and Glutamic acid (286). On the other hand,Metformin showed no interaction with lowest docking score among all.

Three among these four strongest binding showing molecules belongs to the category of anti-viral whereas the Daunorubicin is a chemotherapy drug. Structural analysis of these molecules indicated that all these have multiple oxo- groups in form of amide linkage in all the three anti-viral molecules whereas in Daunorubicin having a special quinone moiety [21]. The amide linkage in Ritonavir and Lopinavir also make the two HIV agents another promising molecules followed by quinone ring containing Atovaquinone.

4. Conclusion

The antiviral drugs (Saquinavir, Nelfinavir and Darunavir) showed the strongest binding efficiency along with chemotherapy drug (Daunorubicin). The HIV drugs also showed good binding efficiency making them a good option after these antiviral molecules. These molecules can be employed until a new molecule with targeted action is not obtained. But the clinical trials are must before recommending a drug for combating the disease and the efforts for developing new drugs with more promising activity must be kept on in the same line.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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