Repurposing of available antiviral drugs against SARS-CoV-2 by targeting crucial replication machinery proteins: a molecular docking study

Ahmed F. El-Sayed[a], Amira T. Mohammed[b], Wafy Hamed[c], Shaymaa Abdelmalek[d]

Departments of [a]Microbial Genetic, [b]Biochemistry, Genetic Engineering and Biotechnology Division, National Research Centre, Giza, [c]Department of Microbiology and Immunology, Faculty of Veterinary Medicine, Sadat University, Menoufia, [d]Department of Microbiology and Immunology, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt

Correspondence to Ahmed F. El-Sayed, PhD in Microbial Genetics, Researcher at Department of Microbial Genetics, Genetic Engineering and Biotechnology Division, National Research Centre, Giza, Egypt. Tel: +20 106 035 0070; e-mail: ahmedfikry.nrc@gmail.com

Received: 23 September 2021
Revised: 25 October 2021
Accepted: 28 October 2021
Published: 24 December 2021

Egyptian Pharmaceutical Journal 2021, 20:371–392

Background and objectives
The newly emerged severe acute respiratory syndrome coronavirus is spreading worldwide rapidly with increasing incidence rates. Due to lack of effective treatments and vaccines, various drug repurposing studies are being developed. Searching for available antiviral drug libraries is the best and fast option to advance to clinical trials and spread their application among infected patients.

Materials and methods
Molecular docking study was performed utilizing AutoDock 4.2 system and Discovery Studio 4.5, which were utilized to predict the activity pocket of the target proteins.

Results and conclusion
The results found that the interacting affinities resulted from the molecular simulation of 3CL protease with ligands Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir were –7.2, –7.4, –7.2, –6.3, –6.1 and –6.6 kcal/mol, respectively. Similarly, the interacting energies obtained from the docking of RNA helicase with ligands were –7.9, –7.4, –6.4, –7.9, –6.2, and –6.9 kcal/mol. Also, the binding energies obtained from the docking of 3′-5′ exoribonuclease with ligands were –10.6, –10.1, –6.5, –7.1, –6.1, and –9.3 kcal/mol. Finally, the binding energies score from the docking of the RNA-dependent RNA polymerase with ligands was –9.6, –6.9, –6.2, –6.6, –6.7, and –6.4 kcal/mol. Based on the binding energy score and docking result, Ledipasvir and Sofosbuvir have a higher affinity of the drug molecule such as against RNA-dependent RNA polymerase, exonuclease, and 3CL protease. Besides, Ledipasvir and Galidesivir show prominent binding interaction with severe acute respiratory syndrome coronavirus RNA helicase. The results are promising for evaluated drugs especially Ledipasvir and Sofosbuvir and could be useful in emergency treatment of coronavirus disease 2019 patients.

Keywords:
3CL protease, coronavirus disease 2019, exonuclease, helicase, molecular docking, RNA-dependent RNA polymerase

Egypt Pharmaceut J 20:371–392

1687-4315

Introduction

A novel human strain of coronavirus severe acute respiratory syndrome coronavirus (SARS-CoV-2) has emerged in Wuhan, China [1]. The WHO has proclaimed the outbreak of coronavirus illness [coronavirus disease 2019 (COVID-19)] a worldwide crisis and a pandemic [2]. COVID-19 is caused by SARS-CoV-2 and can cause symptoms 2–14 days after exposure, with fever, cough, difficulty breathing, general fatigue, loss of taste and/or smell, sore throat, nausea, or vomiting and diarrhea [3,4].

Human coronaviruses, positive-sense single-stranded RNA viruses, have a genome size of about 30 000 bp, which encode the replicate complex (ORF1ab), translated in the form of polyproteins (pp), which contain four structural proteins and 20 nonstructured proteins (NSP). Some of these are NSPs, RNA-dependent RNA polymerase (RdRp) (NSP12), 3CL protease ($3CL^{pro}$), 3′-5′ exoribonuclease, and RNA helicase. The last two enzymes play an important role in replication machinery, replication fidelity, and RNA capping and replication of the longest RNA genomic material of corona viruses [5,6].

RdRp is a vital protein in the replication of RNA viruses, including coronaviruses. It focuses on several types of RNA viruses, including hepatitis C virus (HCV), Zika virus, and coronaviruses [7]. Among

the coronaviruses NSPs, there are two proteases that are vital to virus replication [8]. As part of translational NSPs processing and release, the major protease is known as the 3-C-like protease ($3CL^{pro}$) and the papain-like protease (PL^{pro}), both of which are responsible for the recent coronavirus epidemics of SARS and Middle East respiratory syndrome (MERS) [9]. The main protease (3 CL^{pro}) is a key enzyme in the processing of polyproteins pp1a and pp1ab. ORF1a and ORF1ab are cleaved by papain-like protease (PL^{pro}, nsp3) and 3C-like protease ($3CL^{pro}$, nsp5) [10]. The SARS-CoV $3CL^{pro}$ has an important function and considered an active target for antiviral drugs [11]. $3CL^{pro}$ is the major protease responsible for the control of many major viral functions and has a highly conserved SARS-CoV catalytic domain [12]. Some of its functions include viral replication processes, making it an ideal drug development goal [13].

The SARS epidemic and recent emergence of MERS feature the possible lethality of zoonotic coronavirus diseases in people. No particular antiviral treatment alternatives are accessible [5].

In this investigation, the virtual screening concentrate against the first known SARS-CoV-2 was performed. The obtained results will help in the repurposing of already available marketed Food and Drug Administration (FDA)-approved antiviral drugs, Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir to combat the recent dangerous SARS-CoV-2 nonstructured proteins (RdRp, 3CL protease, exonuclease, and RNA helicase). The antiviral drugs that the FDA has approved, act on nonstructured proteins (nucleotide analogs and polymerase inhibitors). This study helps the scientists to do clinical trials in the field, which gives the hope to the world to fight the newly emerged threatening outbreak.

Materials and methods

Preparation of protein receptors

The two three-dimensional (3D) structures of the coronavirus proteins with their PDB:ID $3CL^{pro}$ (5r7y) and RdRp (6M71) used in our study were downloaded from the Protein Databank. The other two proteins (helicase and exoribonuclease with accession numbers YP_009725308.1 and YP_009725309, respectively) and their amino acid sequences were downloaded from NCBI and modeled to form a 3D structure by Modeler 20.v. All the 3D structures of the objective proteins were performed by erasing the local native drug and water molecules. In addition, polar hydrogen were added according to the amino acid protonation state at pH 7.0 utilizing AutoDock, version 4.2 program. Thereafter, nonpolar hydrogens were merged while polar hydrogens were added to each protein. Repeat this process for each protein, then save it in the pdbqt format and insert it for molecular binding. We then added hydrogen atoms to the molecule using the MG tool in AutoDock Vina4 the Molecular Graphics Lab. at The Scripps Research Institute.

Preparation of ligands

All FDA-approved antiviral inhibitors (Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir) were extracted and collected from ZINC database. The preparation steps of compounds and inhibitors were performed by converting from Structure Data Format to MOL2 chemical format using an Open babel. In addition, nonpolar hydrogen was deleted. Also, polar hydrogen charges were added. Furthermore, the torsions degrees were set to 0. Also using open babel, it was converted to the pdb format. Finally, inhibitor ligands were converted and saved into the dockable pdbqt format through AutoDock tools. The structures of prepared ligands were energy minimized and used as input files for AutoDock 4.2.5.

Docking studies

Docking studies were endeavored to investigate the binding method of the recommended inhibitors onto the 3D model of the protein of SARS-CoV-2 utilizing AutoDock tools 4.2. Before docking, polar-H atoms were added to the SARS-CoV-2 model followed by Gasteiger charge computation utilizing AutoDock devices. The macromolecule files were energy minimized and then saved in the pdbqt format and fit to be utilized for docking. Polar-H charges of the Gasteiger-type were allocated, and nonpolar-H were converged with the carbons. Default settings were utilized for all other parameters. PyMOL package was utilized to visualize the binding cooperation between these ligands with a 3D model of SARS-CoV-2 receptors. All the docking tests were performed utilizing AutoDock Vina as it offers (a) more precision in anticipating ligand–protein cooperation contrasted with its past AutoDock 4.2;(b) more limited running time due to its numerous center processors; and (c) more exactness for ligand handling more than 20 rotatable bonds.

Preparation of a grid box

The receptors file was saved in the pdbqt format. Ligand-centered maps were generated by the

AutoGrid program with a spacing of 0.388 A° and grid dimensions of 90 A°×90 A°×90 A°. Grid box center was set to the coordinates 0.076, 0.093, −0.012 in the x, y, z format, respectively. All the docking tests for helicase and exoribonuclease were finished utilizing the strategy for blind docking (utilizing the grid box sufficiently huge to cover the entire protein structure).

Visualization

The illustration and interpretation of the docking analysis was achieved at the 3D and 2D level of interactions for the COVID protein–drug complex structure by the Discovery Studio 4.5 program. Molecular interactions of amino acids located in the activity pocket and catalytic groves with drug include hydrophobic bonds, hydrophilic bonds, hydrogen bonds, and their bond lengths in the form of graphical representation.

Results

Docking and molecular interaction studies of severe acute respiratory syndrome coronavirus 3CL protease

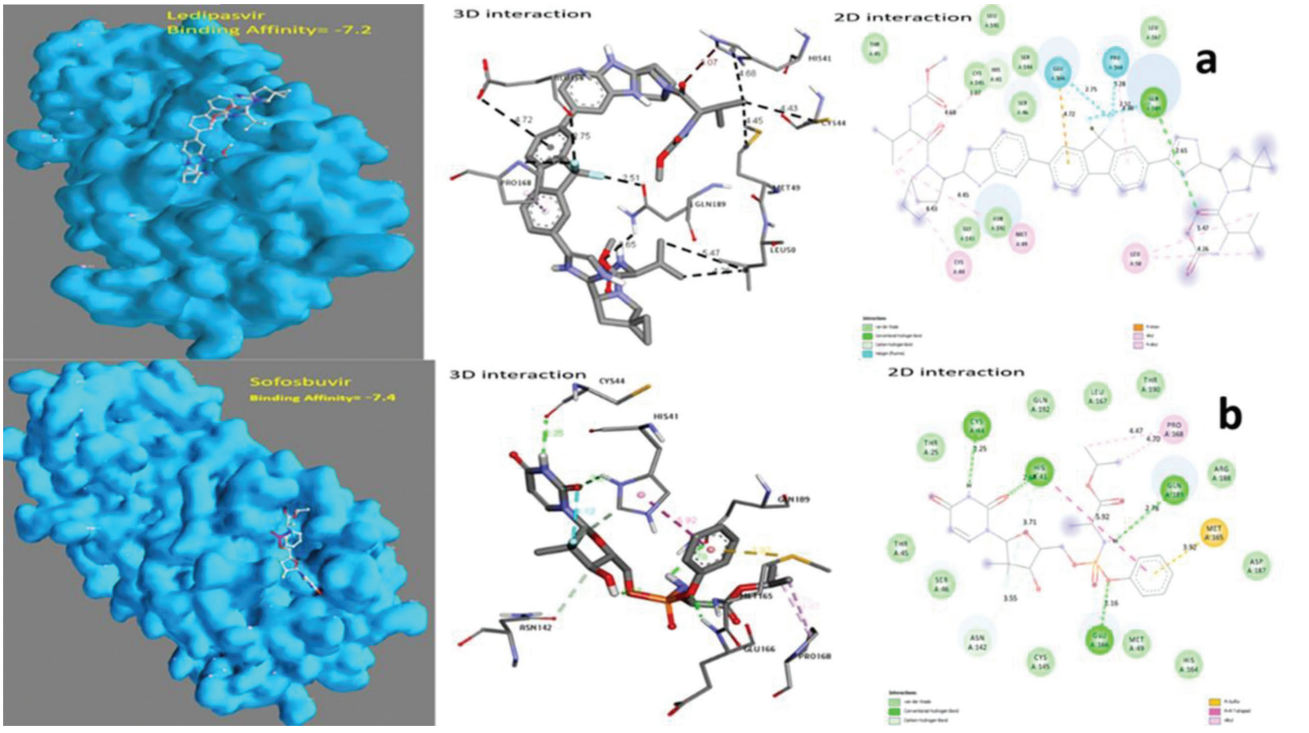
Our results indicated that inhibitor drugs prepared for docking were screened for Lipinski's rule of five as presented in Table 1. All the six potential inhibitors viz. Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir got docked onto the 5R7Y_A 3C-like protease as shown in Fig. 1. The good, recorded binding energy value was obtained for Sofosbuvir (−7.4 kcal/mol). The best pose with the least energy is considered promising because it is very stable for the compound.

On the basis of simulation analysis, data in Table 2 and Fig. 1a show that the docking of Ledipasvir with the SARS-CoV-2 main 3CL protease shows high-affinity interaction −7.2 kcal/mol. Ledipasvir formed one

Table 1 Lipinski's rule screening for physiochemical properties of molecules

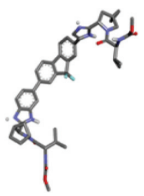
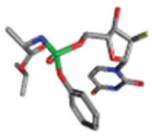
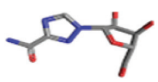
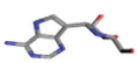
No	Drugs	ZINC ID	M.wt (Da)	H-bond donor	H-bond acceptor	Rotatable bonds	logP
1	Ledipasvir	ZINC000150338819	889.017	4	10	12	7.4
2	Sofosbuvir	ZINC000100074252	529.458	3	11	11	1.6
3	Ribavirin	ZINC000012402860	244.2	4	7	3	-1.8
4	Galidesivir	ZINC000013492903	265.27	6	7	2	-2.1
5	Tenofovir	ZINC000001543475	287.21	3	8	5	-1.6
6	Remdesivir	ZINC000013516399	602.6	4	13	14	1.9

Figure 1



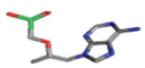
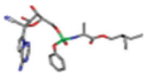
The six drug ligands docked in SARS-CoV-2 main protease (PDB ID 5r7y) with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding of ligands with an amino acid with a hydrogen bond (green dash line). (a) Ledipasivir binding with 3CLpro, (b) Sofosbuvir binding with 3CLpro. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

Table 2 Molecular contact of drugs with residues of 3C-like proteinase (residues having similar contact are red colored and in bold)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
1	3C-like proteinase	Ledipasvir		Gln189	2.65	Leu50 (Alkyl)	5.47	1	10	−7.2
						Leu50 (Alkyl)	4.26			
						Pro168 (Alkyl)	4.38			
						Pro168 (fluorine)	3.28			
						Glu166 (fluorine)	2.75			
						Glu166 (pi-anion)	4.72			
						His41 (Van der Waals)	4.48			
						Cys44 (Alkyl)	4.68			
						Met49 (Alkyl)	4.45			
2		Sofosbuvir		His41	2.68	Asn142 (carbon-H)	3.55	4	10	−7.4
				Cys44	2.25	His41 (Van der Waals)	3.71			
				Glu166	2.16	Pro168 (Alkyl)	4.47			
				Gln189	2.78	Pro168 (Alkyl)	4.70			
						Met165 (Pi-sulfur)	3.92			
						His41 (Pi-pi T shaped)	5.92			
3		Ribavirin		Glu166	2.96	Glu166	2.26	4	6	−7.2
				His163	2.11	Gly143	2.62			
				His164	2.33					
				Phe140	2.32					
4		Galidesivir		Gln189	1.98	His164 (Pi-sigma)	3.76	4	6	−6.3
				Gln189	2.01	Met49 (carbon-H)	3.28			
				Cys44	2.27					
				Arg188	3.03					

(*Continued*)

Table 2 (***Continued***)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
5		Tenofovir		Glu166	2.68	Asn142 (carbon-H)	3.11	5	6	−6.1
				Glu166	2.69					
				Arg188	2.04					
				His164	3.03					
				Leu141	2.62					
6		Remdesivir		His41	2.50	His41 (Van der Waals)	3.56	3	7	−6.6
				Glu166	1.98	Asn142 (Alkyl)	3.48			
				Gln189	2.38	Met165 (Pi-sulfur)	3.93			
						Pro168 (Alkyl)	4.07			

3D, three-dimensional.

hydrogen bond with Gln189. Also, Ledipasvir formed nine nonhydrogen bond interactions within the activity pocket; five alkyl bonds with residues Leu50, Pro168, Cys44, and Met49, two halogen (fluorine) bonds formed with Pro168 and Glu166, and only one π-anion contact with Glu166.

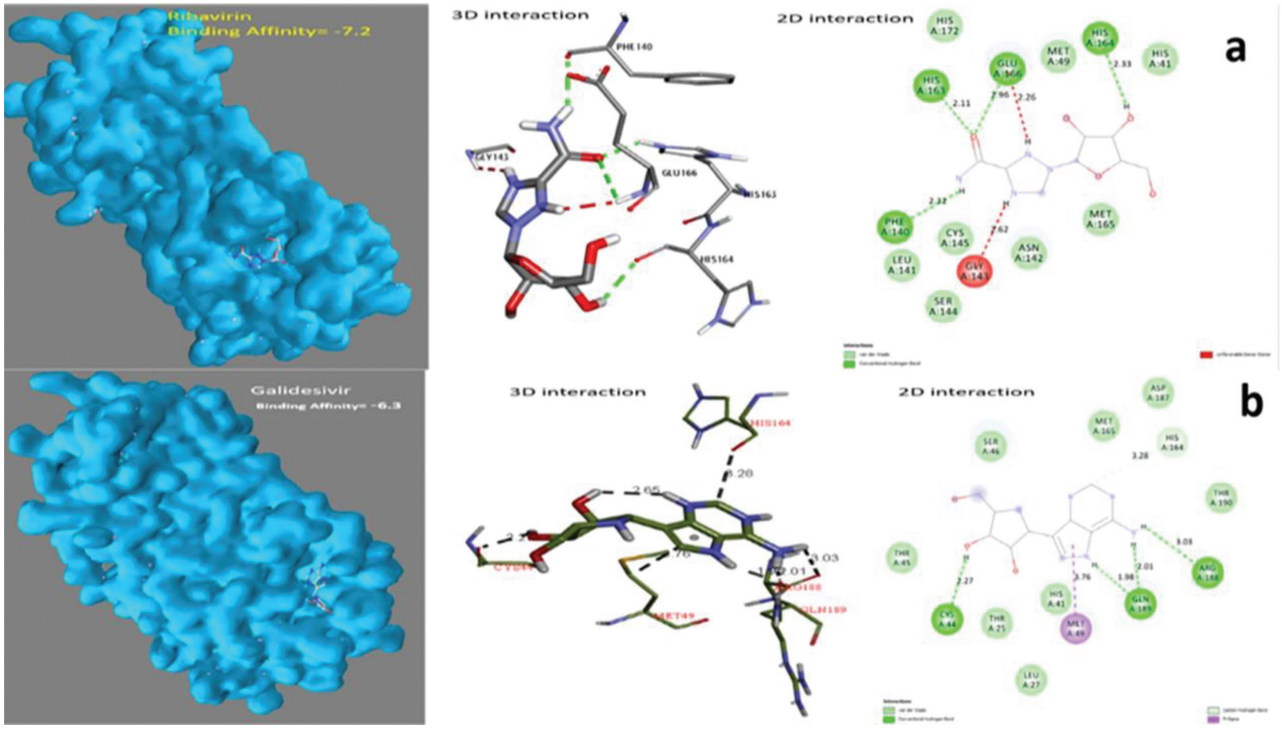
Data shown in Fig. 1b illustrated that the interaction of Sofosbuvir with the SARS-CoV-2 main 3CL protease in complex shows the highest affinity interaction (7.4 kcal/mol). Also, we noticed that four H bonds were formed with His41, Cys44, Glu166, and Gln189. Besides, six non-H-bonds were formed with Asn142 (Carbon-H), His41 (Van der Waals bond), Pro168 (Alkyl), Pro168 (Alkyl), Met165 (Pi-sulfur), and His41 (Pi-pi T shaped). Results were obtained by docking of Ribavirin with the SARS-CoV-2 main 3CL protease Fig. 2a show high-affinity interaction −7.2 kcal/mol. Ribavirin formed four H-bonds with His41, Cys44, Glu166, and Gln189 and six hydrophobic reactions with Asn142 (carbon-H), His41 (Van der Waals), Pro168 (Alkyl), Pro168 (Alkyl), Met165 (Pi-sulfur), and His41 (Pi-pi T shaped). Also, Fig. 2b shows that the docking of Galidesivir with the SARS-CoV-2 main 3CL protease shows moderate-affinity interaction with the chain A of protein with an affinity of −6.3 kcal/mol. Galidesivir formed four H bonds with Gln189, Gln189, Cys44, and Arg188 and two hydrophobic reactions with His164 (Pi-sigma) and Met49 (carbon-H).

The docking of Tenofovir with 3CL protease in the complex has the least affinity interaction −6.1 kcal/mol. Tenofovir created five H bonds with Glu166, Arg188, His164, and Leu14, one hydrophobic reaction with Asn142 (carbon-H) (Fig. 3a). Docking of Remdesivir with the SARS-CoV-2 main 3CL protease shows moderate affinity interaction −6.6 kcal/mol. As shown in Fig. 3b, it has three H bonds with His41, Glu166, and Gln189. Also, four hydrophobic reactions with His41 (Van der Waals), Asn142 (Alkyl bond), Met165 (π-sulfur), and Pro168 (Alkyl). Finally, our data indicated that comparison of the docking analysis of six inhibitors find that the most common residues Gln189, Glu166, and His164 in the activity and binding pocket increase the interactions of all six compounds through the formation of H bonds.

Docking and molecular interaction studies of severe acute respiratory syndrome coronavirus RNA helicase

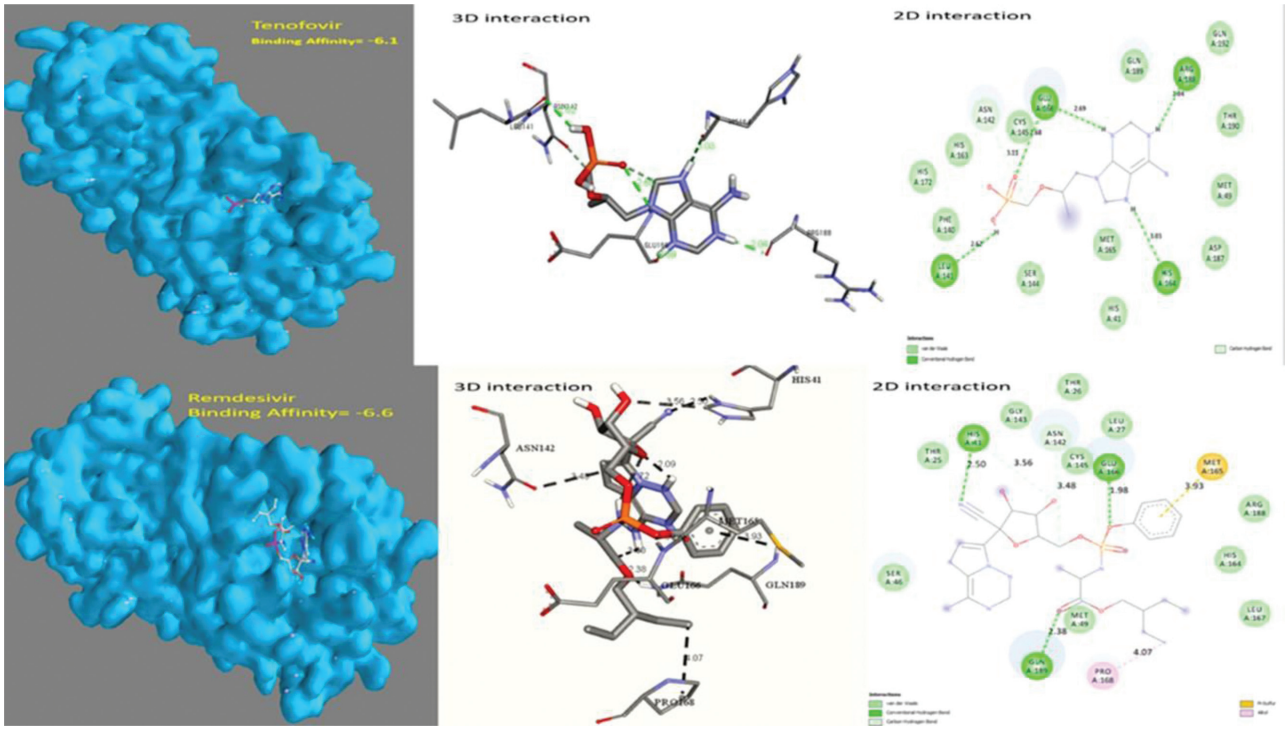
Our data obtained from this simulation supported and enhanced the suitable binding of the promising drug inhibitors Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir against the predicted 3D model of SARS-CoV-2 RNA helicase enzyme with docking score (binding energy). Our results show the binding of amino acids that take

Figure 2



The six drug ligands docked in SARS-CoV-2 main protease (PDB ID 5r7y) with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional interaction amino acid residues involved in the interaction (with ligand as color sticks) and 2D interaction binding of ligands with an amino acid with a hydrogen bond (green dash line) (a) Ribavirin binding with 3CLpro, (b) Galidesivir binding with 3CLpro. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

Figure 3

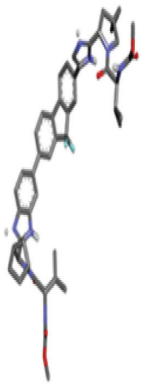


The six drug ligands docked in SARS-CoV-2 main protease (PDB ID 5r7y) with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding of ligands with an amino acid with a hydrogen bond (green dash line). (a) Tenofovir binding with 3CLpro, (b) Remdesivir binding with 3CLpro. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

part in the drug–protein interactions. The result of the binding energy from the docking analysis of Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir to the 3D model of helicase is represented in Table 3.

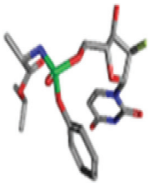
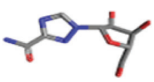
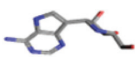
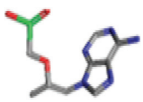
The docking of Ledipasvir with the SARS-CoV-2 RNA helicase enzyme has the highest affinity interaction with a binding of −7.9 kcal/mol. No H bonds were formed by Ledipasvir. But Ledipasvir formed 18 nonhydrogen bond interactions within

Table 3 Molecular contact of drugs with residues of three-dimensional model of severe acute respiratory syndrome coronavirus helicase (residues having similar contact are red colored and in bold)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H-bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
1	3D model of SARS-CoV-2 RNA Helicase	Ledipasvir		–	–	Ala553 (Pi-Alkyl)	5.20	-	18	−7.9
						Ala553 (halogen)	3.61			
						Ala553 (unfavorable)	2.01			
						Val558 (Pi-Alkyl)	5.47			
						Val558 (Alkyl)	4.26			
						Val558 (Alkyl)	4.38			
						Val456 (Alkyl)	3.28			
						Thr416 (Pi-sigma)	4.75			
						Leu455 (Alkyl)	3.38			
						Leu581 (Alkyl)	4.54			
						Arg560 (unfavorable)	4.69			
						His554 (pi-anion)	4.81			
						Cys556 (carbon-H)	3.84			
						Leu412 (Alkyl)	4.59			
						Leu412 (Alkyl)	4.25			
						Tyr457 (Alkyl)	4.59			
						Lys584 (Alkyl)	4.47			
						Lys584 (Alkyl)	4.87			

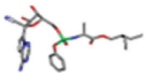
(*Continued*)

Table 3 (***Continued***)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H-bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
2		Sofosbuvir		Asn179	2.04	Leu412 (Alkyl)	4.65	4	15	–7.4
				Arg560	2.52	Leu417 (Alkyl)	4.24			
				Arg560	2.11	Ala407 (Amidepi-stacked)	4.97			
				Asp534	2.52	Pro406 (Alkyl)	4.09			
						Pro406 (Pi-Alkyl)	5.22			
						Arg409 (Alkyl)	3.70			
						Pro408 (Alkyl)	4.74			
						Pro408 (Pi-Alkyl)	3.99			
						Arg560 (pi-anion)	3.97			
						Asp534 (pi-anion)	3.65			
						Phe422 (Alkyl)	4.90			
3		Ribavirin		Asn557	2.57	–	–	3	3	–6.4
				Ala407	2.57					
				Leu417	2.38					
4		Galidesivir		Leu417	2.39	Asn559 (unfavorable)	3.76	8	8	–7.9
				Leu417	2.41	Pro406 (Pi-Alkyl)	3.28			
				Leu412	1.96					
				Leu412	2.16					
				Asn557	2.25					
5		Tenofovir		Asn557	2.27	Leu417 (Alkyl)	4.23	8	12	–6.2
				Asn557	2.09	Pro406 (Alkyl)	4.33			
				Asn559	2.42	Phe422 (Alkyl)	5.22			
				Leu412	1.88	Thr410 (Van der Waals)	2.90			
				Leu412	2.76					

(*Continued*)

Table 3 (***Continued***)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H-bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
6		Remdesivir		Leu417	2.10					
				Leu417	2.47					
				Arg409	2.15					
				His554	2.96	His554 (Pi-Alkyl)	4.70	4	9	−6.9
				His554	2.53	Arg560 (pi-Cation)	3.79			
				Leu412	2.03	Phe422 (Alkyl)	5.12			
				Arg560	5.30	Pro406 (Alkyl)	3.79			
						Pro408 (Pi-Alkyl)	4.11			

3D, three-dimensional; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

the activity pocket, Ala553 (Pi-Alkyl), Ala553 (halogen), Ala553 (unfavorable bump), Val558 (Pi-Alkyl), Val558 (Alkyl), Val558 (Alkyl), Val456 (Alkyl), Thr416 (Pi-sigma), Leu455 (Alkyl), Leu581 (Alkyl), Arg560 (unfavorable bump), His554 (pi-anion), Cys556 (carbon-H), Leu412 (Alkyl), Leu412 (Alkyl) Tyr457 (Alkyl), Lys584 (Alkyl), and Lys584 (Alkyl) as shown in Table 3 and Fig. 4a.

Also, the docking of Sofosbuvir with the 3D model of SARS-CoV-2 helicase shows high affinity interaction −7.4 kcal/mol. Also, we noticed that four H bonds were formed with Asn179, Arg560, Arg560, and Asp534. Besides, 11 non-H-bonds were formed with Leu412 (Alkyl), Leu417 (Alkyl), Ala407 (Amide pi-stacked), Pro406 (Alkyl), Pro406 (Pi-Alkyl), Arg409 (Alkyl), Pro408 (Alkyl), Pro408 (Pi-Alkyl), Arg560 (pi-anion), Asp534 (pi-anion), and Phe422 (Alkyl) as presented in Fig. 4b.

Results in Fig. 5a show the docking of Ribavirin with the 3D model of SARS-CoV-2 helicase showing moderate-affinity interaction −6.4 kcal/mol. Ribavirin have three H bonds with Asn557, Ala407, and Leu417but no hydrophobic interaction. The docking of Galidesivir with the 3D model of helicase for SARS-CoV-2 shows the same affinity as that of Ledipasvir (−7.9 kcal/mol). Galidesivir formed four H bonds with Gln189, Gln189, Cys44, and Arg188 and two hydrophobic reactions with His164 (Pi-sigma) and Met49 (carbon-H) as presented in Fig. 5b. Also, the docking of Tenofovir with the model of helicase shows the least-affinity interaction −6.2 kcal/mol. Tenofovir formed eight H bonds with Asn557, Asn559, Leu412, Leu417, and Arg409 and four hydrophobic reactions with Leu417 (Alkyl) Pro406 (Alkyl), Phe422 (Alkyl), and Thr410 (Van der Waals) (Fig. 6a). Data in Fig. 6b illustrates the docking of Remdesivir with the model of helicase has a slightly better affinity interaction −6.9 kcal/mol. It formed three H bonds with His41, Glu166, and Gln189 and four hydrophobic reactions with His41 (Van der Waals), Asn142 (Alkyl bond), Met165 (π-sulfur), and Pro168 (alkyl).

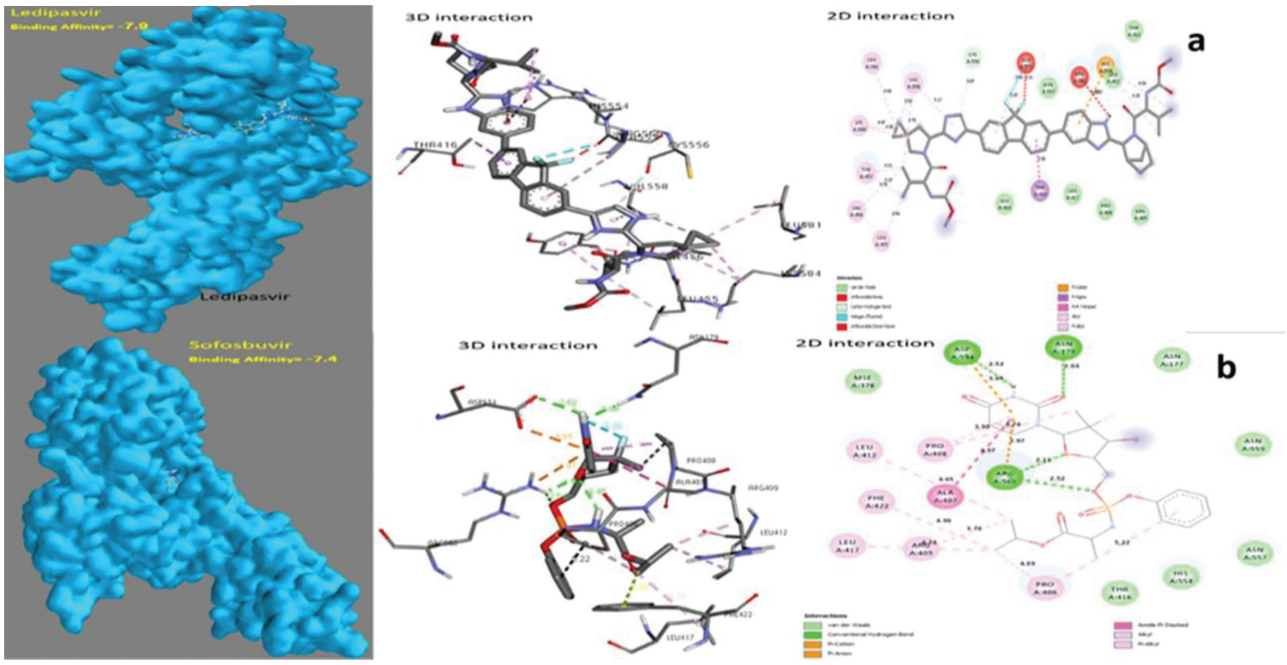
Various residues included in the ligand–helicase interactions are shown as a stick with red color. From our simulation analysis, it is concluded that the residues Arg560, Leu412, and Leu417 in the pocket cavity increase the interaction of all the six drugs by the creation of H bonds.

Docking and molecular interaction studies of severe acute respiratory syndrome coronavirus 3′-5′ exoribonuclease

Our data of the binding affinity from the simulation study of Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir to exoribonuclease for SARS-CoV-2 is represented in Table 4.

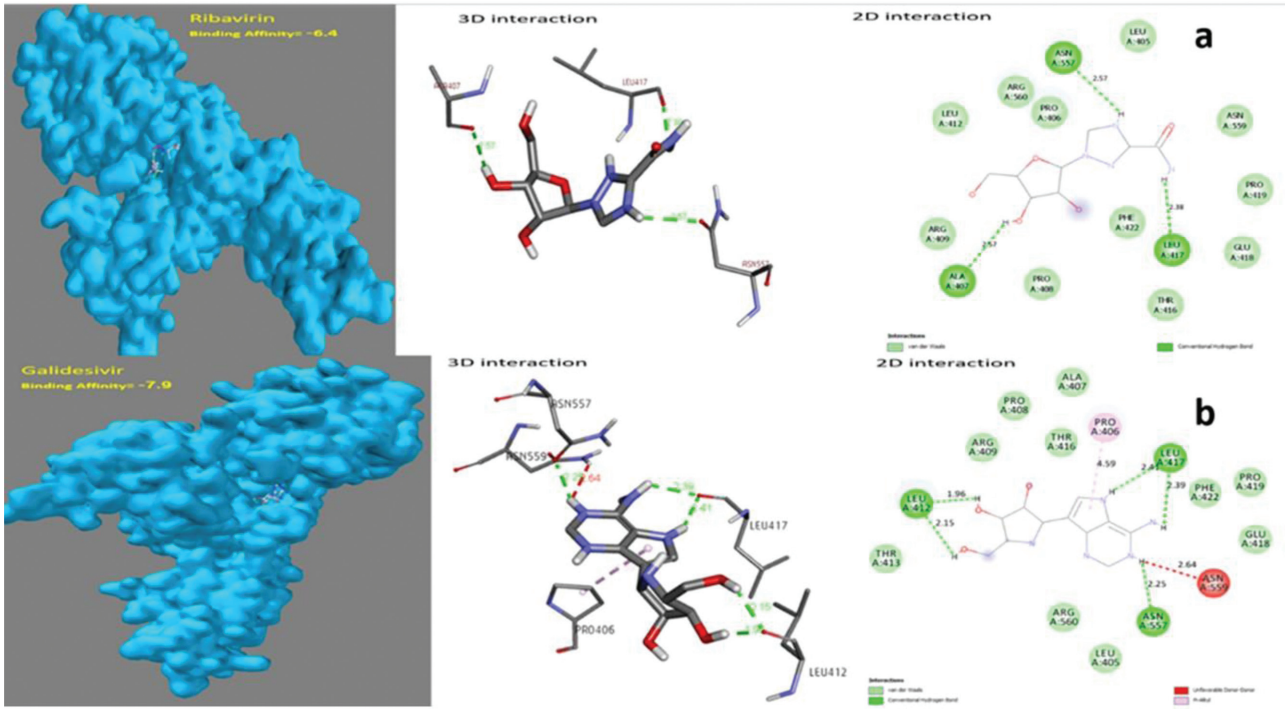
Results obtained by Table 4, and Fig. 7a show the docking of Ledipasvir with the SARS-CoV-2 3′-5′ exoribonuclease in the complex has the greatest affinity interaction −10.6 kcal/mol. Ledipasvir created four H bonds with Asn386, Asn386, Gln313, and Arg289 and Ledipasvir formed 22 nonhydrogen bond interactions within the activity pocket, seven alkyl bonds with

Figure 4



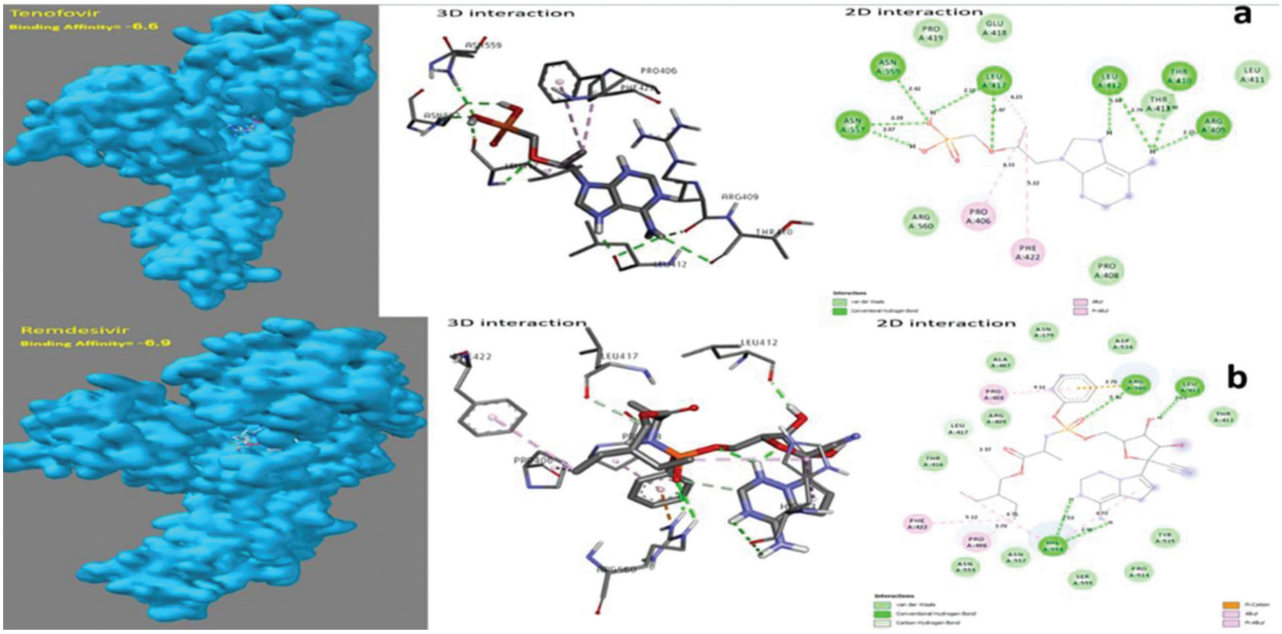
The six drug ligands docked in three-dimensional (3D) model of SARS-CoV-2 helicase with the best binding mode in the pocket of a protein (with ligand as color sticks), 3D interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding of ligands with an amino acid with a hydrogen bond (green dash line). (a) Ledipasivir binding with SARS-CoV-2 helicase, (b) Sofosbuvir binding with SARS-CoV-2 helicase. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

Figure 5



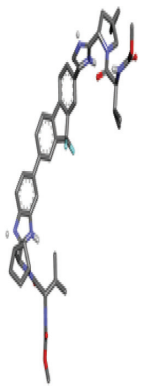
The six drug ligands docked in three-dimensional (3D) model of SARS-CoV-2 helicase with the best binding mode in the pocket of a protein (with ligand as color sticks), 3D interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding of ligands with an amino acid with a hydrogen bond (green dash line). (b) Ribavirin binding with SARS-CoV-2 helicase, (b) Galidesivir binding with SARS-CoV-2 helicase. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

Figure 6



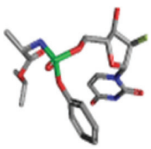
The six drug ligands docked in three-dimensional (3D) model of SARS-CoV-2 helicase with the best binding mode in the pocket of a protein (with ligand as color sticks), 3D interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding interaction of ligands with an amino acid with a hydrogen bond (green dash line). (a) Tenofovir binding with SARS-CoV-2 helicase, (b) Remdesivir binding with SARS-CoV-2 Helicase. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

Table 4 Molecular contact of drugs with residues of severe acute respiratory syndrome coronavirus 3′-5′ exoribonuclease (residues having similar contact are red colored and in bold)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
1	Exonuclease	Ledipasvir		Asn386	2.31	Pro429 (Alkyl)	7.31	4	26	−10.6
				Asn386	2.96	Pro342 (Alkyl)	4.11			
				Gln313	2.69	Pro342 (Alkyl)	4.24			
				Arg289	2.61	Ala553 (halogen)	4.55			
						Val290 (Pi-Alkyl)	5.06			
						Val290 (Alkyl)	4.89			
						Val287 (Alkyl)	3.84			

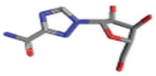
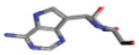
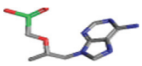
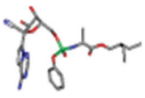
(*Continued*)

Table 4 (*Continued*)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
						Asn386 (Halogen)	3.43			
						Trp385 (Halogen)	2.74			
						Ile338 (Pi-Alkyl)	4.15			
						Ile338 (Alkyl)	5.48			
						Arg289 (Pi-Alkyl)	3.77			
						His427 (pi-anion)	4.73			
						Arg310 (pi-cation)	4.27			
						Arg310 (pi-cation)	4.47			
						Arg310 (Pi-Alkyl)	4.82			
						Arg310 (Alkyl)	5.15			
						Cys387 (Pi-Alkyl)	4.92			
						Phe367 (Pi-Alkyl)	4.48			
						Phe426 (Pi-Pi T shape)	4.83			
						Cys387 (Pi-pi H bond)	3.67			
						Lys339 (Van der Waals)	3.67			
2		Sofosbuvir		Asn388	1.85	Val290 (Alkyl)	5.78	4	15	−10.1
				Asn388	1.86	Arg289 (Alkyl)	3.68			
				Tyr368	2.34	Phe426 (Pi-Pi T shape)	4.29			
				Ala553	2.05	Asp352 (Halogen)	4.73			
						Phe367 (Pi-Pi stacked)	5.21			
						Tyr368 (unfavorable)	2.41			
						Pro429 (Alkyl)	4.19			
						His427 (Alkyl)	5.47			
						Val287 (Alkyl)	4.75			
						Ala553 (Pi-Alkyl)	4.39			
						Asn386 (Van der Waals)	3.49			

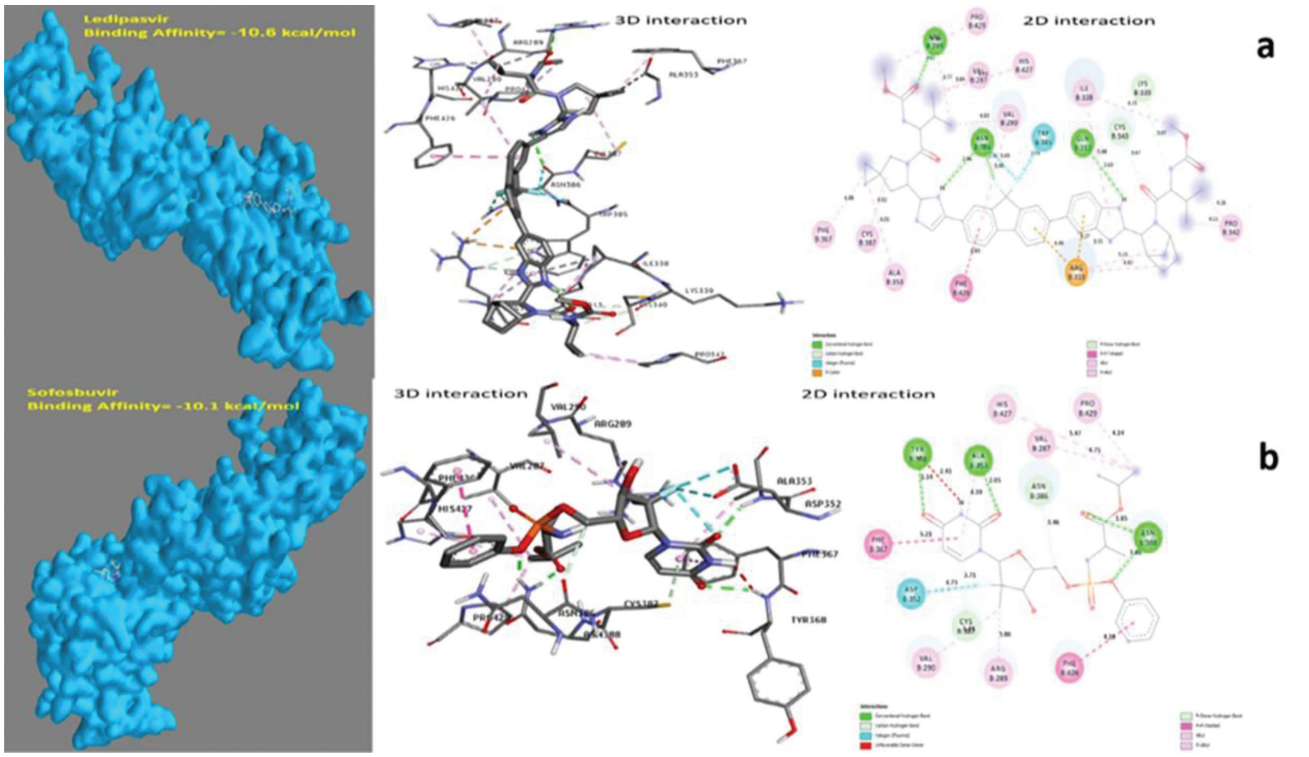
(*Continued*)

Table 4 (***Continued***)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
3		Ribavirin		Gln354	2.00	Ala553 (unfavorable)	2.79	7	9	−6.5
				Asp352	2.12	Gln354 (unfavorable)	2.04			
				Asn388	2.39					
				Asn388	2.55					
				Asn388	2.91					
				Asn386	2.12					
				Tyr368	3.68					
4		Galidesivir		Ala553	3.68	Val290 (Pi-Alkyl)	5.90	5	8	−7.1
				Ala553	3.33	Asn388 (H-Bond)	2.03			
				Asn386	5.43	His427 (pi-anion)	4.33			
				Leu366	5.26					
				Tyr368	5.65					
5		Tenofovir		Asp331	2.24	Trp385 (unfavorable)	1.79	5	8	−6.1
				Gln313	2.52	Lys336 (Alkyl)	4.78			
				Trp385	2.68					
				Gly333	2.66					
				Ile332	2.54					
6		Remdesivir		Asn388	2.87	Ala353 (Pi-Alkyl)	5.01	6	16	−9.3
				Asn388	2.11	Val389 (Pi-Alkyl)	5.45			
				Leu366	2.95	Cys387 (Pi-Alkyl)	4.90			
				Asp352	2.11	Phe367 (Pi-Alkyl)	4.71			
				Asn386	2.50	Pro335 (Pi-Alkyl)	5.22			
				Asn386	3.07	Pro335 (Alkyl)	4.48			
						Val290 (Pi-Alkyl)	5.10			
						Trp292 (Alkyl)	5.17			
						Trp385 (Alkyl)	3.84			
						Asn388 (unfavorable)	1.38			

3D, three-dimensional.

Figure 7



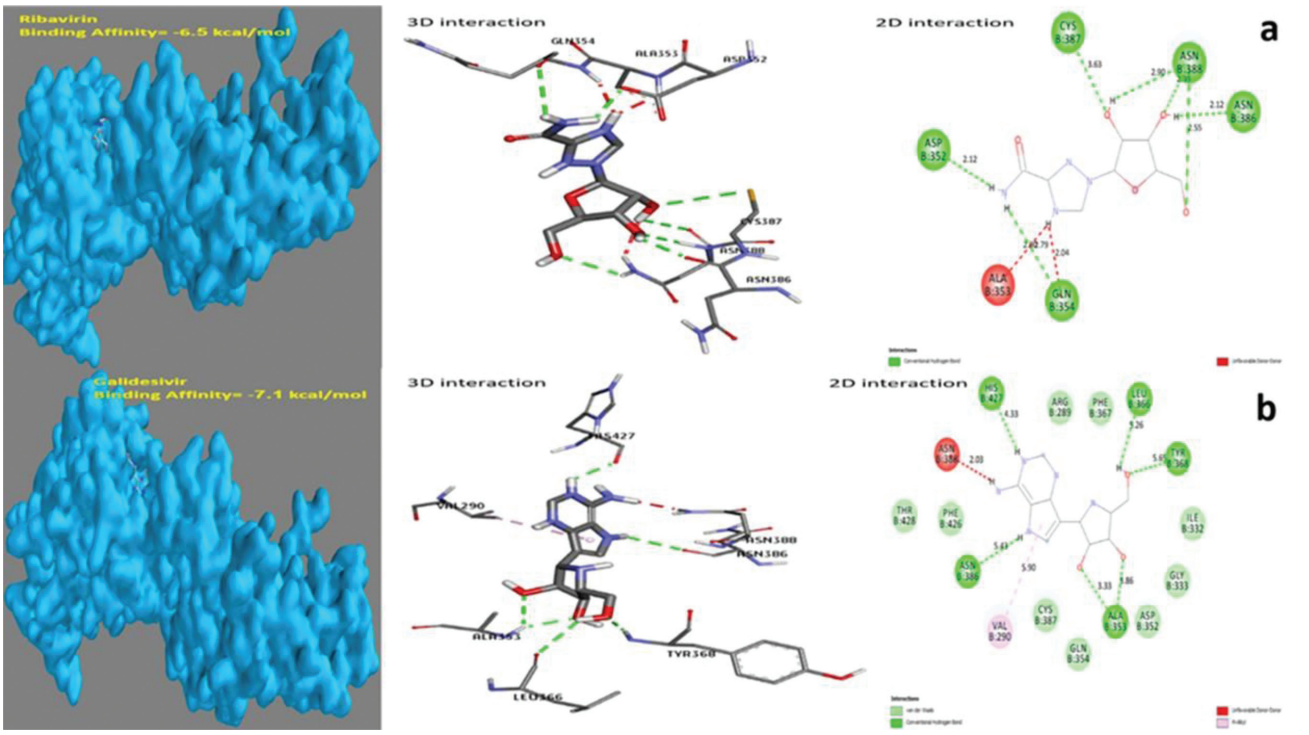
The six drug ligands docked in SARS-CoV-2 3′-5′ exoribonuclease with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional (3D) interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding interaction of ligands with an amino acid with a hydrogen bond (green dash line). (a) Ledipasivir binding with SARS-CoV-2 3′-5′ exoribonuclease, (b) Sofosbuvir binding with SARS-CoV-2 3′-5′ exoribonuclease. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

residues Pro429, Pro342, Pro342, Val290, Val287, Ile338, and Arg310, three halogen (fluorine) bonds formed with Ala553, Asn386, and Trp385, five pi-alkyl bonds with residues Val290, Ile338, Arg289, Arg310, and Cys387, and only one Van der Waals contact with Lys339. Data in Fig. 7b shows the docking of Sofosbuvir with the SARS-CoV-2 3′-5′ exoribonuclease in the complex showing very high-affinity interaction −10.1 kcal/mol. Also, we noticed that four H bonds were formed with Asn388, Asn388, Tyr368, and Ala553. Besides, 11 non-H-bonds were formed with Val290 (Alkyl), Arg289 (Alkyl), Phe426 (Pi-Pi T shape), Asp352 (Halogen), Phe367 (Pi-Pi stacked), Tyr368, (unfavorable Bond), Pro429 (Alkyl), His427 (Alkyl), Val287 (Alkyl), Ala553 (Pi-Alkyl), and Asn386 (Van der Waals).

Results obtained by Fig. 8a show that the docking of Ribavirin with the SARS-CoV-2 3′-5′ exoribonuclease in the complex shows low-affinity interaction −6.5 kcal/mol. Ribavirin formed seven H bonds with Gln354, Asp352, Asn388, Asn386, and Tyr368 and two hydrophobic reactions with Ala553 (unfavorable bond) and Gln354 (unfavorable bond). Also Fig. 8b shows that the docking of Galidesivir with the SARS-CoV-2 3′-5′ exoribonuclease in the complex shows moderate-affinity interaction −7.1 kcal/mol. Galidesivir made six H bonds with Ala553, Asn386, and Leu366 and three hydrophobic reactions with Val290 (pi-alkyl), Asn388 (carbon–H-bond), and His427 (pi-anion). The docking of Tenofovir with the SARS-CoV-2 3′-5′ exoribonuclease in the complex shows the least affinity interaction −6.1 kcal/mol. Tenofovir formed five H bonds with Asp331, Gln313, Trp385, Gly333, and Ile332 and two hydrophobic reactions with Trp385 (unfavorable bond) and Lys336 (alkyl), (Fig. 9a). Data in Fig. 9b indicate that docking of Remdesivir with the SARS-CoV-2 3′-5′ exoribonuclease in the complex shows high-affinity interaction −9.3 kcal/mol. It formed six H bonds with Asn388, Leu366, Asp352, and Asn386 and10 hydrophobic reactions with Ala353 (pi-alkyl), Val389 (pi-alkyl), Cys387 (Pi-alkyl), Phe367 (Pi-Alkyl), Pro335 (pi-alkyl), Pro335 (alkyl), Val290 (pi-alkyl), Trp292 (alkyl), Trp385 (alkyl), and Asn388 (unfavorable bond).

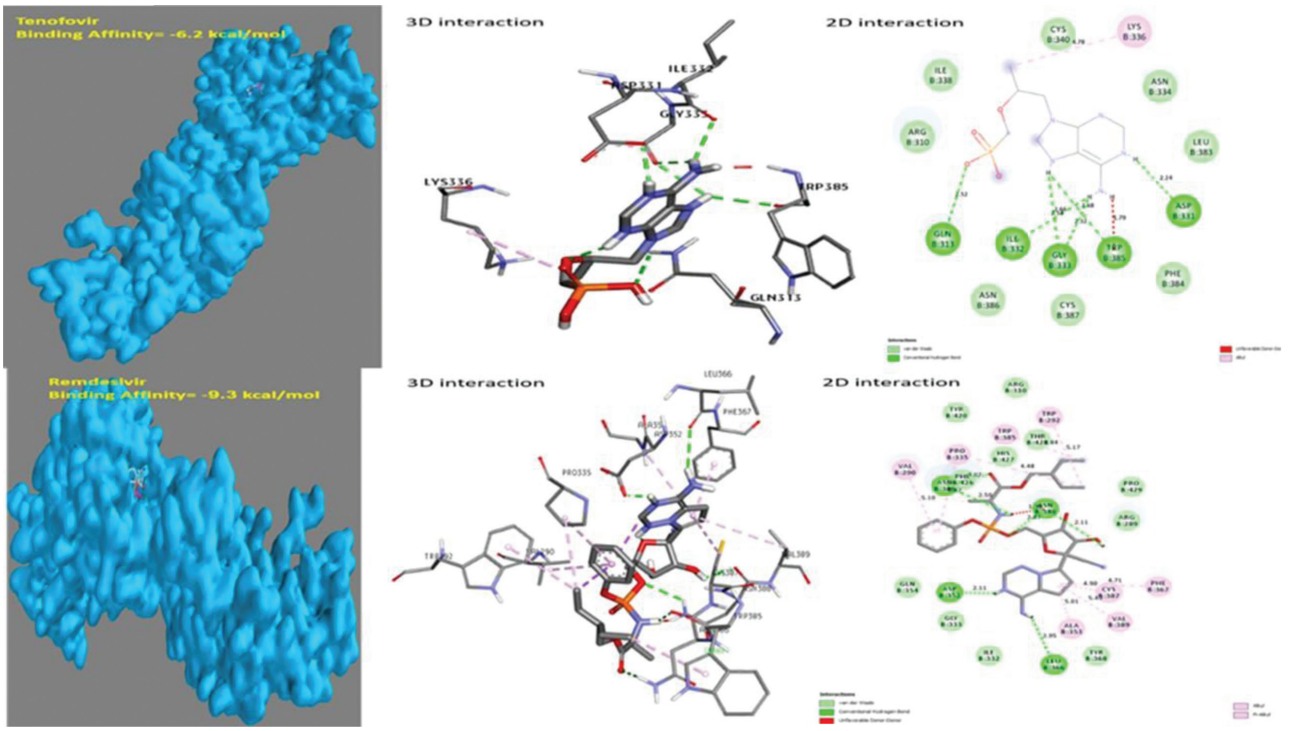
All residues included in the drug–exonuclease complex are illustrated as bold with red color. Our studies

Figure 8



The six drug ligands docked in SARS-CoV-2 3′-5′ exoribonuclease with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional (3D) interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding of ligands with an amino acid with a hydrogen bond (green dash line). (a) Ribavirin binding with SARS-CoV-2 3′-5′ exoribonuclease, (b) Galidesivir binding with SARS-CoV-2 3′-5′ exoribonuclease. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

Figure 9



The six drug ligands docked in SARS-CoV-2 3′-5′ exoribonuclease with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional (3D) interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding of ligands with an amino acid with a hydrogen bond (green dash line). (a) Tenofovir binding with SARS-CoV-2 3′-5′ exoribonuclease, (b) Remdesivir binding with SARS-CoV-2 3′-5′ exoribonuclease. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

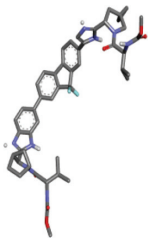
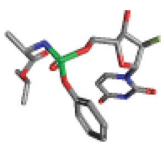
supported the fact that residues Asn386, Tyr368, and Gln313 enhanced the binding interaction in the catalytic site by the formation of bonds. The best results were obtained for exonuclease inhibitors Ledipasvir and Sofosbuvir, with free-binding energies of −10.6 and −10.1 kcal/mol, respectively, followed by the Remdesivir and Galidesivir with −9.3 and −7.1 kcal/mol.

Docking and molecular interaction studies of RNA-dependent RNA polymerase (NSP12)

Data obtained in this molecular analysis of Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir to RdRp of the novel SARS-CoV-2 is represented in Table 5. Out of the six drugs, Ledipasvir and Sofosbuvir were used as promising inhibitors and represented the highest interactions with catalytic pocket residues of RdRp.

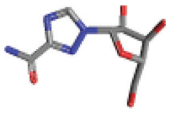
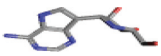
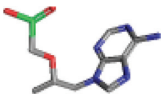
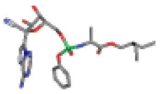
The result in Fig. 10a showed the docking of Ledipasvir with RdRp, which have the greatest affinity interaction −9.6 kcal/mol. Ledipasvir formed two H bonds with Asp623 and Arg553. Furthermore, Ledipasvir has nine nonhydrogen bond interactions within the activity pocket, with Ala685 (Pi-Alkyl), Ala688 (Pi-Alkyl), Val560 (Alkyl), Ser682

Table 5 Molecular contact of drugs with amino acids of RNA-dependent RNA polymerase (residues having similar contact are red colored and in bold)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
1	RNA-dependent RNA polymerase	Ledipasvir		Asp623	2.18	Ala685 (Pi-Alkyl)	5.05	2	15	−9.6
				Arg553	2.62	Ala688 (Pi-Alkyl)	5.41			
						Ala688 (Pi-Alkyl)	4.76			
						Val560 (Alkyl)	5.27			
						Val560 (Alkyl)	5.24			
						Ser682 (Halogen)	2.76			
						Ser501 (carbon H)	3.56			
						Asp760 (H-bond)	4.87			
						Arg555 (Alkyl)	3.67			
						Arg555 (Alkyl)	3.83			
						Arg624 (Alkyl)	4.71			
						Lys621 (Alkyl)	4.59			
						Asp623 (carbon H)	3.62			
2		Sofosbuvir		Asn691	2.53	Asp623 (pi-anion)	4.43	8	11	−6.9

(*Continued*)

Table5 (*Continued*)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
				Asp623	2.74	Lys621 (pi-cation)	2.37			
				Arg553	2.55	Thr556 (Halogen)	3.16			
				Arg553	2.97					
				Lys621	2.99					
				Ser682	2.38					
				Thr556	2.38					
				Cys622	2.38					
3		Ribavirin		Arg624	2.69	Asp623 (Va nd Waals)	3.85	9	11	−6.2
				Arg624	4.61	Ser682 (unfavorable)	2.10			
				Thr556	2.91					
				Thr556	2.96					
				Thr556	2.69					
				Ala554	2.95					
				Asp452	2.38					
				Thr556	2.77					
				Tyr456	2.65					
4		Galidesivir		Asp760	2.09	Thr556 (carbon H-bond)	3.13	4	7	−6.6
				Asp760	2.59	Asp760 (unfavorable)	2.70			
				Asp623	2.23	Asp760 (pi-anion)	3.84			
				Thr556	2.87					
5		Tenofovir		Thr556	2.19	Arg555 (Alkyl)	4.17	9	11	−6.7
				Thr556	2.27	Asp623 (carbon H)	3.75			
				Asp452	1.82					
				Ala554	2.45					
				Arg553	4.14					
				Arg624	2.74					
				Asp623	2.51					
				Thr680	3.71					
				Ser681	2.31					
6		Remdesivir		Arg624	2.27	Asp760 (pi-anion)	4.22	8	10	−6.4
				Ser682	2.77	Tyr619 (H-bond)	3.24			
				Lys621	2.23					
				Lys621	2.77					

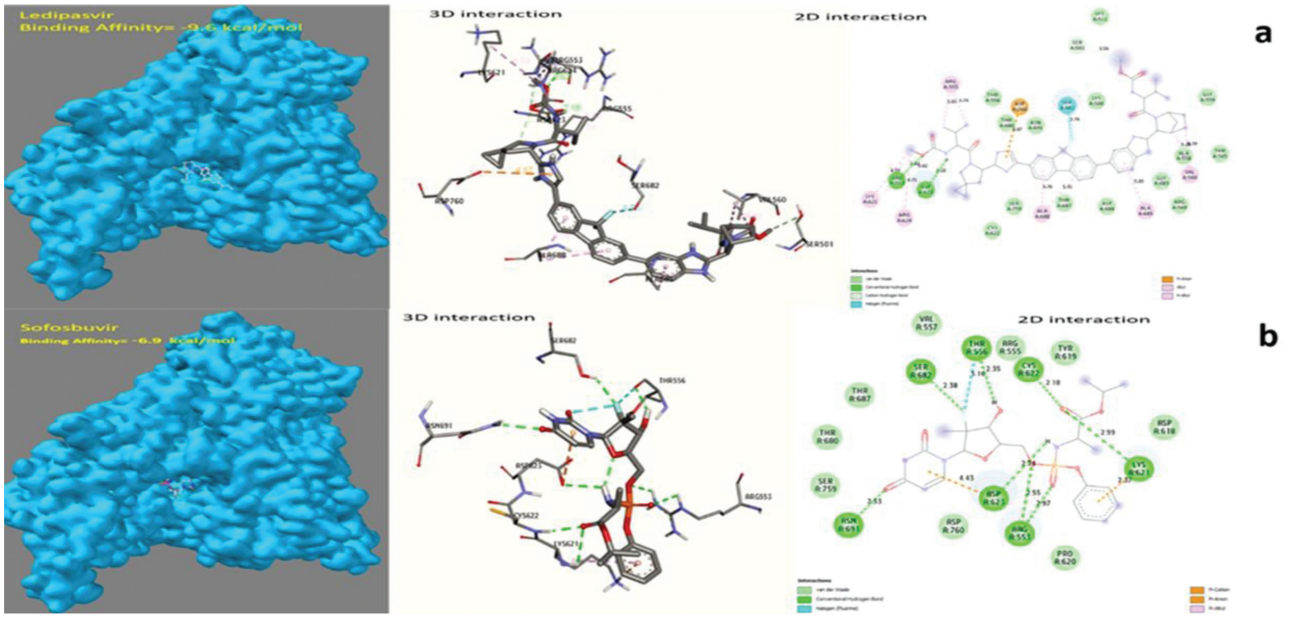
(*Continued*)

Table5 (*Continued*)

No.	Protein	Drugs	3D structure	Hydrophilic interactions		Hydrophobic contacts		Number of H bonds	Number of total bonds	Binding affinity (kcal/mol)
				Residue (H-bond)	Length (A°)	Residue (bond type)	Length (A°)			
				Asp761	3.05					
				Asp760	4.35					
				Asp760	1.95					
				Tyr619	2.57					

3D, three-dimensional.

Figure 10



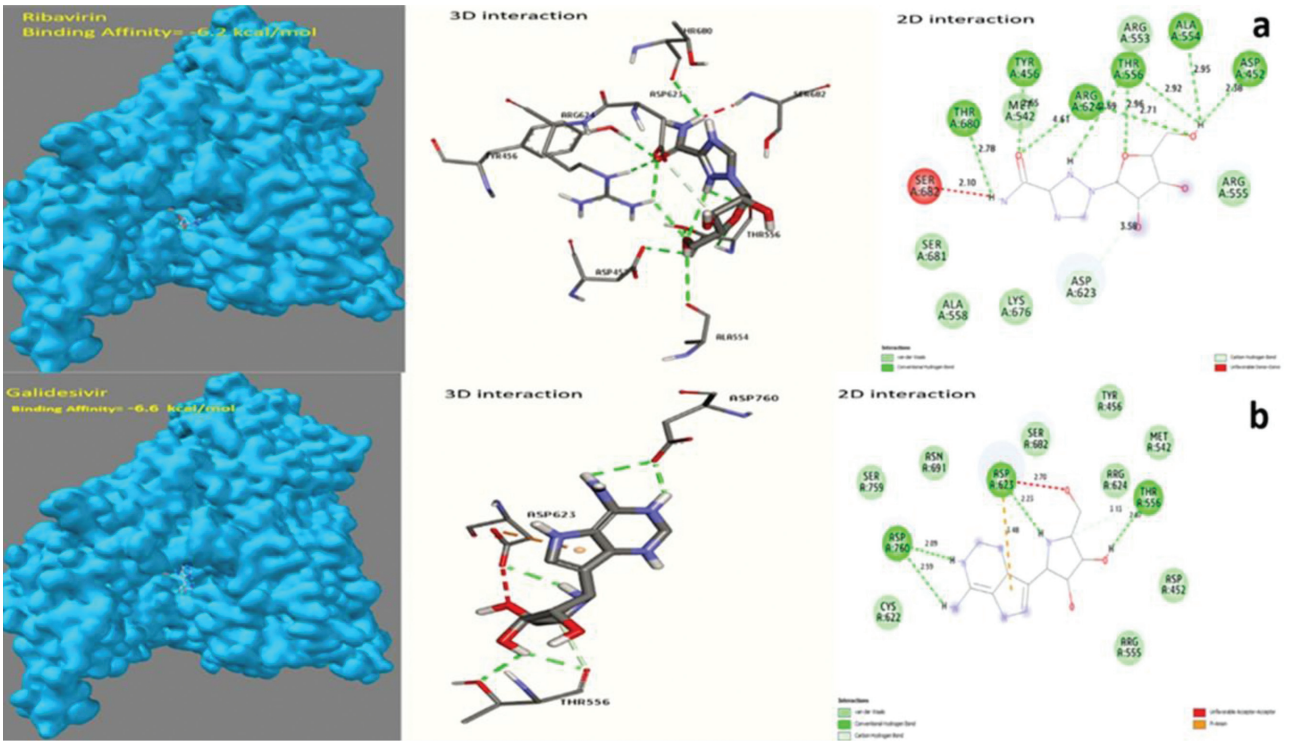
The six drug ligands docked in SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional (3D) interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding of ligands with an amino acid with a hydrogen bond (green dash line). (a) Ledipasivir binding with SARS-CoV-2 RdRp, (b) Sofosbuvir binding with SARS-CoV-2 RdRp. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

(halogen), Ser501 (carbon H-Bond), Asp760 (carbon H-Bond), Arg555 (Alkyl), Arg624 (Alkyl), Lys621 (Alkyl), and Asp623 (carbon H-bond).

Also Fig. 10b illustrated that the docking of Sofosbuvir with RdRp has high-affinity interaction −6.9 kcal/mol. Also, we noticed that eight H bonds were formed with Asn691, Asp623, Arg553, Lys621, Ser682, Thr556, and Cys622. Besides, three non-H-bonds were formed with Asp623 (pi-anion), Lys621 (pi-cation), and Thr556 (halogen). Results obtained by Fig. 11a showed that the docking of Ribavirin with COVID-19 (RdRp) have the least affinity interaction −6.2 kcal/mol. Ribavirin formed nine H bonds with Arg624, Thr556, Ala554, Asp452, Thr556, and Tyr456, and also two hydrophobic reactions with Asp623, (Van der Waals) and Ser682 (unfavorable bond). Besides, Fig. 11b shows that the docking of Galidesivir with the COVID-19 (RdRp) shows moderate-affinity interaction with an affinity of −6.6 kcal/mol. Galidesivir formed four H bonds with Asp760, Asp760, Asp623, and Thr556 and three hydrophobic reactions with Thr556 (carbon H-bond), Asp760 (unfavorable bond), and Asp760 (pi-anion).

The docking of Tenofovir with COVID-19 (RdRp) shows slightly good affinity interaction −6.7 kcal/mol. Tenofovir formed nine H bonds with Thr556, Thr556, Asp452, Ala554, Arg553, Arg624, Asp623, Thr680, and Ser681 and two hydrophobic reactions with Arg555 (Alkyl) and Asp623 (carbon H-Bond) as presented in Fig. 12a). Figure 12b shows that the docking of Remdesivir with (RdRp) shows

Figure 11



The six drug ligands docked in SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional (3D) interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding interaction of ligands with an amino acid with a hydrogen bond (green dash line). (a) Ribavirin binding with SARS-CoV-2 RdRp, (b) Galidesivir binding with SARS-CoV-2 RdRp. RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

moderate-affinity interaction −6.4 kcal/mol. It formed eight H bonds with Arg624, Ser682, Lys621, Asp761, Asp760, and Tyr619 and two hydrophobic reactions with Asp760 (pi-anion) and Tyr619 (carbon H-bond). Different residues included in the compound–target interactions are in red bold illustration. Our studies supported that residues Asp623, Arg624, Thr556, and Asp760 enhanced the binding interaction in the catalytic site by the formation of bonds. The best results were obtained for RdRp inhibitors Ledipasvir and Sofosbuvir −9.6 and −6.9 kcal/mol, respectively, followed by Tenofovir and Galidesivir with −6.7 and −6.6 kcal/mol, respectively.

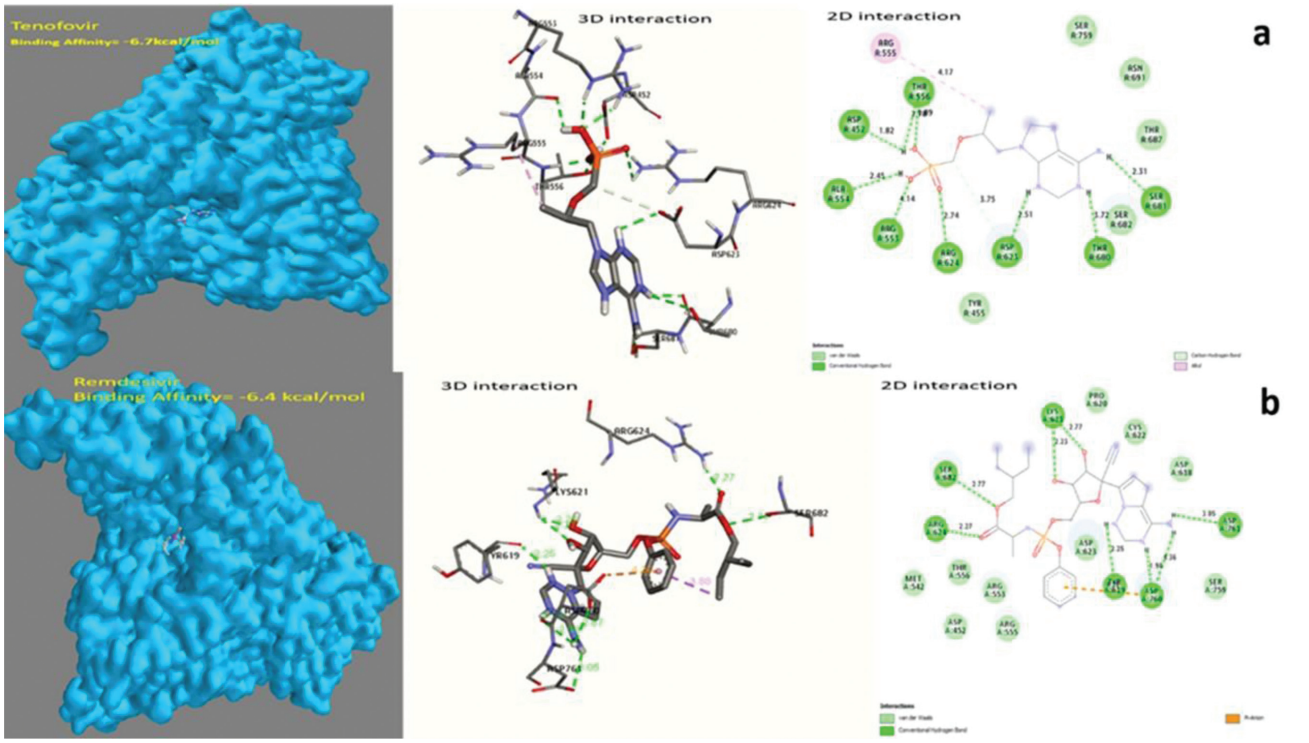
Discussions

Alarming outbreak of COVID-19 was caused by SARS-CoV-2. First discovered in Wuhan, Hubei, China the mode of transmission is human to human through air droplets. The WHO reported this illness as a global public health emergency on February 15, 2020 [14].

FDA has not approved any antiviral medications for the treatment of COVID-19. All clinical treatments are guided toward symptomatic treatment. Several studies have developed promising drug candidates that can reduce COVID-19 symptoms by inhibiting certain components of SARS-CoV-2. For example, Remdesivir showed adverse effects against SARS-CoV-2 [15]. There is currently no safe drug candidate against the SARS and MERS viruses because the epidemic has ended and no clinical trials have been conducted [8].

Our study is a molecular simulation study against the first known SARS-CoV-2. The obtained results will help in the repurposing of the already available antiviral drugs Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir to combat the recent dangerous SARS-CoV-2 NSPs ($3CL^{pro}$, RNA helicase, and 3′-5′ exoribonuclease, and RdRp). The antiviral drugs such as Ledipasvir (NS5A inhibitor of HCV), Sofosbuvir (NS5B RNA polymerase inhibitor of HCV), nucleotide analogs as Ribavirin, Galidesivir, Remdesivir, and Tenofovir (HIV-1 and HBV reverse transcriptase inhibitor). RdRp is an essential enzyme in the replication of RNA viruses; hence, it is a main target in treatment of viral infections, including HCV, ZIKV, and CoVs [16]. The active site of RdRp is

Figure 12



The six drug ligands docked in SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) with the best binding mode in the pocket of a protein (with ligand as color sticks), three-dimensional (3D) interaction amino acid residues involved in the interaction (with ligand as color sticks) and two-dimensional interaction binding of ligands with an amino acid with a hydrogen bond (green dash line). (a) Tenofovir binding with SARS-CoV-2 RdRp, (b) Remdesivir binding with SARS-CoV-2 RdRp. SARS-CoV-2, severe acute respiratory syndrome coronavirus.

highly similar, with two successive and surface-accessible aspartates in a beta-turn structure [17].

The protein 3-chimotrypsin like SARS-CoV ($3CL^{pro}$) has been shown to be important for replication and has therefore been recognized as an important drug target for SARS infection. $3CL^{pro}$ inhibitors have been discovered during the last 12 years from many sources as structure-based molecular docking studies. This perspective is a good guide for researchers to use SARS-CoV $3CL^{pro}$ inhibitors as anti-SARS chemotherapy [18]. The $3CL^{pro}$ enzymes are the preferred routes for the immediate treatment of coronaviruses ;and other coronavirus proteins could be targeted for virtual screening [8].

RdRp is the essential enzyme for RNA virus regeneration [19]. In mammalian positive-strand RNA (+RNA) viruses, the enzyme is produced by transcription of the recorded viral genome, which provides a polyprotein precursor that is released by the RdRp-containing subunit by proteolytic cleavage. RdRp is then embedded in a membrane containing viral enzymes that drive the production of new RNA (–RNA) and genome molecules [20]. RNA viral genome is translated with low fidelity because the reproductive product is thought to be untested and unchanged [21]. This property is an important part of the evolution, modification, and proliferation of RNA viruses. 3′-5′ exoribonuclease (nsp14) is one of the replication mechanisms, which interacts with nsp7/nsp8/nsp12.

All these nonstructured proteins help in the replication of long coronavirus RNA. The nsp14 is responsible for the viral RNA capping and the viral genome proofreading to safeguard coronavirus replication fidelity, so all replication machinery proteins that are associated with the RdRp are targets for antiviral drug developments. This complex is important in RNA polymerization, proofreading, and cap-modifying into a multifunctional protein assembly. This macromolecular assembly with RNA helicase (nsp13) shares to form the core of the coronavirus replication machinery, which can engage in coordinated RNA synthesis and processing activities. The RNA helicase (nsp13) is a multifunctional protein, which is able to use the dsDNA and dsRNA as substrates with 5′-3′ polarity, plus it can also work with nsp12 in the viral genome replication machinery and included in viral RNA assembly and associates with nucleoproteins in the membrane complex [5].

We concentrated on the action, receptors, and side effects of six available drugs, Ledipasvir, Sofosbuvir, Ribavirin, Galidesivir, Tenofovir, and Remdesivir. Ledipasvir is approved in combination with Sofosbuvir for the treatment of chronic HCV genotype 1 (Harvoni). Sofosbuvir nowadays is considered as an inhibitor for SARS-CoV-2 based on the similarity between RdRp of HCV and coronaviruses. Both are positive-sense RNA viruses and similar in replication machinery [22]. The dual-component HCV drugs, Harvoni, may be attractive candidates to repurpose because they may inhibit two coronavirus enzymes. Targeting two viral proteins reduces viral resistance. Harvoni has very few side effects and is easy to administer [8]. No toxicity measurements are required because they were tested previously by FDA and no dose recommendation for patients with renal failure [22].

Ribavirin is a nucleotide analog FDA-approved drug for the treatment of chronic HCV in combination with interferon alfa-2b, but this drug is teratogenic, embryonic, and not suitable for cardiac patients. Galidesivir is an approved drug for the treatment of HCV and Ebola virus, which shows broad-spectrum antiviral action against many RNA viruses. Ribavirin is screened virtually against SARS and MERS suggesting strong effectiveness [23]. Tenofovir is an approved drug for HIV-1 and HBV treatment, which is used in adults and the young (2 years of age). But Tenofovir side effects are decreased bone mineral density and immune reconstitution syndrome. COVID-19 treatment with Remdesivir showing improved patients has just been reported, and clinical trial is now underway [24]. The presence of FDA-approved anti-RdRp drugs helps treat patients and reduces the risk of new SARS-CoV-2 infection. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir are potent drugs against SARS-CoV-2 because they strongly bind to RdRp [25].

The current study found that the molecular docking and interaction between the six available drug candidates with $3CL^{pro}$ of SARS-CoV-2 show a good interaction and better fit to the $3CL^{pro}$ enzyme. It is an excellent drug target as it has more than one binding sites. Also, the results obtained by this study showed that Sofosbuvir is the most suitable ligand for $3CL^{pro}$ with the highest interactions (−7.4 kcal/mol). The interaction affinity of the used six drug ligands in the descending manner is Sofosbuvir, Ledipasvir, and Ribavirin with high interaction (−7.2 kcal/mol), then Galidesivir and Remdesivir are with moderate interaction (−6.3 kcal/mol) and (−6.6 kcal/mol), respectively. Tenofovir shows the least interaction affinity (−6.1 kcal/mol); $3CL^{pro}$ targeting reported that Harvoni (Ledipasvir /Sofosbuvir) could be promising medication against COVID-19 [8].Another important finding is that all six available drug candidates interact with specific residues in activity groves of SARS-CoV-2 RNA helicase enzyme. The results show that Ledipasvir and Galidesivir have the highest binding affinity (−7.9 kcal/mol). Sofosbuvir shows high affinity (−7.4 kcal/mol) and Remdesivir has slightly good binding affinity of −6.9 kcal/mol. Ribavirin has moderate interaction (−6.4 kcal/mol), but Tenofovir has the least interaction (−6.2 kcal/mol). A surprising finding is that the best results were obtained for SARS-CoV-2 3′-5′ exoribonuclease inhibitors, Ledipasvir and Sofosbuvir, with free binding energies of −10.6 and −10.1 kcal/mol, respectively, followed by Remdesivir and Galidesivir with −9.3 and −7.1 kcal/mol. Ribavirin shows moderate interaction affinity of −6.5 kcal/mol and Tenofovir has the least interaction affinity of −6.1 kcal/mol.

Our study proved the effectiveness of Ledipasvir and Sofosbuvir to inhibit RdRp protein. The promising data were obtained for RdRp inhibitors, Ledipasvir and Sofosbuvir, with free interacting energies of −9.6 and −6.9 kcal/mol, respectively, followed by Tenofovir of slightly good binding affinity of −6.7 kcal/mol; however, Galidesivir and Remdesivir were with moderate binding of −6.6 and −6.4 kcal/mol, respectively. Ribavirin has the least binding power of −6.2 kcal/mol. Modeling and docking for SARS-CoV-2 RdRp and targeting by anti-polymerase drugs such as Sofosbuvir, Ribavirin, and Remdesivir were performed, and it has been reported that these drugs are effective against the newly emerged viral infections such as COVID-19. Many of the FDA-approved anti-RdRp drugs could inhibit COVID-19 with no toxicity measurements required [25]. According to the data explained above, our study found that all six drug candidates bind to the used four proteins effectively and the Harvoni (Ledipasvir and Sofosbuvir) gave the best binding affinity with all proteins in this study. That is means that Ledipasvir and Sofosbuvir have broad-spectrum effect on replication machinery proteins of new emerged SARS-CoV-2.

The strength points of our work: (a) using in-silico prediction of the effect of our six selected available safe FDA-approved antiviral candidates to inhibit four nonstructured proteins of the SARS-CoV-2 replication machinery. (b) These proteins are so

important in coronaviruses' replication, so inhibition of these proteins could stop viral multiplication and infectivity. (c) The selected drugs are marketed, available, and safe drugs especially Ledipasvir and Sofosbuvir with no side effects and no toxicity according to FDA approval sheets. (d) Most of these selected drugs are multiple viral protein inhibitors that prevent the coronavirus antiviral resistance. *In-silico* study results need to be applicable through experimental and clinical trials. Infected patients should be recruited for clinical trials. Our future study is using the same selected drug candidates and other approved antivirals to be trailed in silico by molecular docking against more nonstructured SARS-CoV-2 proteins such as nsp7 and nsp8.

Conclusion

The disease caused by the novel coronavirus SARS-CoV-2 originated at Wuhan city of China and has been spreading at a fast pace all over the world. Because of the absence of successful treatment choices for SARS-CoV-2, different procedures are being considered. Our study proved *in silico* that Harvoni (Ledipasvir and Sofosbuvir) is a broad-spectrum anti-SARS-CoV-2 drug with minimal side effects and no toxicity and safe for chronic disease patients with hepatic and renal failure. It is suitable for old and young alike. We recommend using Harvoni in emergency treatment of COVID-19 patients.

Acknowledgements

Authors' contributions: A.F.E., the corresponding author, molecular docking and in silico study specialist, manuscript drafting. A.T.M., coauthor, manuscript drafting, manuscript revising. S.A., coauthor design of the work, interpretation of the results, manuscript drafting, and revising. W.H., coauthor, design of the study, manuscript revising. All authors have read and approved the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MU, Khan K. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. J Travel Med 2020; 27: taaa008.

2 Organization WH. Surveillance case definitions for human infection with novel coronavirus (nCoV), interim guidance, 15 January 2020. World Health Organization, 2020.

3 Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, *et al.* The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health – the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020; 91:264–266.

4 Parry J. China coronavirus: cases surge as official admits human to human transmission. British Medical Journal Publishing Group. 2020; 368:236.

5 Subissi L, Posthuma CC, Collet A, Zevenhoven-Dobbe JC, Gorbalenya AE, Decroly E, *et al.* One severe acute respiratory syndrome coronavirus protein complex integrates processive RNA polymerase and exonuclease activities. Proc Natl Acad Sci 2014; 111:E3900–E3909.

6 Elfiky AA, Mahdy SM, Elshemey WM. Quantitative structure-activity relationship and molecular docking revealed a potency of anti-hepatitis C virus drugs against human corona viruses. J Med Virol 2017; 89:1040–1047.

7 Elfiky AA, Elshemey WM. IDX-184 is a superior HCV direct-acting antiviral drug: a QSAR study. Med Chem Res 2016; 25:1005–1008.

8 Chen YW, Yiu C-PB, Wong K-Y. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL pro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. F100Res 2020; 9:129.

9 Kandeel M, Altaher A, Alnazawi M. Molecular dynamics and inhibition of MERS CoV papain-like protease by small molecule imidazole and aminopurine derivatives. J Lett Drug Design Discov 2019; 16:584–591.

10 Li S-W., Lin C-WJB. Human coronaviruses: clinical features and phylogenetic analysis. BioMedicine 2013; 3:43–50.

11 Konno H, Onuma T, Nitanai I, Wakabayashi M, Yano S, Teruya K, Akaji K. Synthesis and evaluation of phenylisoserine derivatives for the SARS-CoV 3CL protease inhibitor. Bioorg Med Chem Lett 2017; 27:2746–2751.

12 Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. J Sci 2003; 300:1763–1767.

13 Bacha U, Barrila J, Velazquez-Campoy A, Leavitt SA, Freire E. Identification of novel inhibitors of the SARS coronavirus main protease 3CLpro. J Biochem 2004; 43:4906–4912.

14 Chan JF-W., Yuan S, Kok K-H., To KK-W., Chu H, Yang J, *et al.* A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395:514–523.

15 Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. Comput Struct Biotechnol J 2020; 18:784–790.

16 Elfiky AA, Elshemey WM. Molecular dynamics simulation revealed binding of nucleotide inhibitors to ZIKV polymerase over 444 nanoseconds. J Med Virol 2018; 90:13–18.

17 Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci 2020; 248:117477.

18 Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung S-H. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. J Med Chem 2016; 59:6595–6628.

19 Cameron CE, Götte M, Raney KD. Viral genome replication. Germany: Springer; 2009.

20 Jones-Burrage SE, Tan Z, Li L, Zlotnick A, Mukhopadhyay S. Identification of Chikungunya virus nucleocapsid core assembly modulators. bioRxiv 2019; 1:774943.

21 Domingo E, Escarmís C, Sevilla N, Moya A, Elena SF, Quer J, *et al.* Basic concepts in RNA virus evolution. FASEB J 1996; 10:859–864.

22 Chien M, Anderson TK, Jockusch S, Tao C, Li X, Kumar S, *et al.* Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. J Proteome Res 2020; 19:4690–4697.

23 Elfiky AA. Zika viral polymerase inhibition using anti-HCV drugs both in market and under clinical trials. J Med Virol 2016; 88:2044–2051.

24 Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, *et al.* First case of2019 novel coronavirus in the United States. N Engl J Med 2020; 382:929–936.

25 Elfiky AA. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. Life Sci 2020; 253:117592.