EJMO

DOI: 10.14744/ejmo.2020.94995
EJMO 2020;4(4):324–335

Research Article

Molecular Docking Study of Some Nucleoside Analogs against Main Protease of SARS-CoV-2

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Abstract

Objectives: The global pandemic outburst of SARS-CoV-2 in December 2019 infected a large number of people and hasclaimed a significant number of lives. Given the lack of proper therapeutic agents or vaccinefor this pandemic disease, the world is faced with a huge challenge of curingthe infected patients. Therefore, the development of potential therapeutic agents against COVID-19 is a dire need of the situation.

Methods: Herein, we utilized molecular docking to explore the inhibitory potential of nine nucleoside analogs, includingTelbivudine, Entecavir, Clevudine, Zalcitabine, Taribavirin, Stavudine, Lamivudine, Cordycepin, and cordycepin triphosphate, against the main protease of SARS-CoV-2.

Results: The binding energy (ΔG) ofthenine nucleoside analogs against the main protease of SARS-CoV-2 were −6.5 Kcal/mole (Telbivudine), −6.8 Kcal/mole (Entecavir), −6.8 Kcal/mole (Clevudine), −5.8 Kcal/mole (Zalcitabine),−6.1 Kcal/mole (Taribavirin), −6.5 Kcal/mole (Stavudine), −5.7 Kcal/mole (lamivudine),−6.5 Kcal/mole(Cordycepin), and −6.9 Kcal/mole (Cordycepin triphosphaye).

Conclusion: Although the molecular docking results are promising, further *in vitro* and *in vivo* studies are required to understand the mechanism of binding of thesenucleoside analogs to the COVID-19 Protein.

Keywords: Binding energy, COVID-19, Molecular Docking, nucleoside analog, SARS-CoV-2 protease

Cite This Article: *Chhetri A, Brahman D. Molecular Docking Study of Some Nucleoside Analogs against Main Protease of SARS-CoV-2. EJMO 2020;4(4):324–335.*

SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) or corona virus disease 2019 (COVID-19) was reported from Wuhan city of China in December 2019 and the viral infection has been spreading rapidly around the world thereby making serious problems to the public health.[1] The World Health Organization (WHO), on March 11, 2020, recognized the disease as a global pandemic due to risingconcern about its fast spreading andcapacity to transmit fromhuman to human.[2] Like SARS-CoV, SARS-CoV-2 or COVID-19 belongs to the β genus of single strand enveloped RNA virus (family of Coronaviridae), which is responsible for acute lung injury accompanied by acute respiratory distress syndrome.[3] Early scientific investigations have shown that the entry of SARS-CoV as well as SARS-CoV-2 into the host cell occurs through the binding of the viral envelope-anchored spike protein with the host receptor ACE2 (angiontensin-converting enzyme 2), thereby causing the infection in the host.[4] There is still no vaccine or definite therapeutic agents for the treatment of the infection caused by SARS-CoV-2.[5] Several antiviral and antimalarial drugs, such as Favipiravir (Influenza), Ribavirin (RSV infection and hepatitis C infection), Nelfinavir (HIV infection), Lopinavir/ritonavir (HIV infection), remdesivir (Hepatitis Cand Sars-CoV-2 infection), Umifenoviror Arbidol (Influenza), Chloroquine, and Hydroxychloroquine (malaria), have been used for the preliminary treatment of COVID-19.[6-11] Recently, a combination of three drugs, Lopinavir, Oseltamivir, and Ritonavirhas been formulated as a therapeutic measure to manage the virulence to a great extent in COVID-19patients (The Scientist, February 3 2020,

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Submitted Date: October 11, 2020 **Accepted Date:** November 10, 2020 **Available Online Date:** December 25, 2020

https://www.the-scientist.com/news-opinion/flu-andanti-hiv-drugs-show-efficacy-against-coronavirus-67052). However, these antiviral or antimalarial drugs have some limitations for the treatment of COVID-19. More over, so far, there is no specific drug against COVID-19approved by the US Food and Drug Administration Agency.[12,13] There fore,-given the global pandemic situation, the world is in need of highly efficient, minimal side effect, inexpensive, and readily available drugs against COVID-19. After the outburst of COVID-19, different research groups have been continuously working in designing and formulating antiviral drugs and vaccine to ascertain the therapeutic strategies for COVID-19.[14-22] Many of these research groups have reported the binding affinity of different natural products, fungal secondary metabolites, FDA approved antiviral or antimalarial drugs, and food supplements, among others, toward the main protease (6LU7) of COVID-19 through Molecular Docking approach.[22-36] On the other hand, nucleoside analogs are, in recent times, found as a backbone of many drugs for the treatment of infection diseases caused by HIV, hepatitis B or C viruses, and herpes viruses.[37,38] Interestingly, biological activity as well as the chemical and physical properties of nucleoside analog can be tuned remarkably by simple alteration of the sugar moiety of nucleoside with different substituent and heteroatom, among others.[39] Moreover, the nucleoside analogs usually show antiviral activities by inhibiting the viral replication through theblockage of cellular division or impairment of DNA/RNA synthesis or inhibition of cellular or viral enzymes activity.[40,41] The nucleoside analogs Telbivudine (hepatitis B inhibiotor), Entecavir (HIV/ AIDS and Hepatitis B inhibitor), Clevudine (Hepatitis B inhibitor), Zalcitabine (reverse-transcriptase inhibitor), Taribavirin (prodrug of Ribavirin), Stavudine (HIV/ AIDS inhibitors), Lamivudine (first-generation nucleoside reverse transcriptase inhibitor), Cordycepin (RNA synthesis inhibitor), and Cordycepin Triphosphate (polyadenylation inhibitors, antineoplastic, antioxidant, and anti-inflammatory agent) have been used in thetreatment ofmany viral diseases.[42-52] In recent times, bioinformatics have provided an alternative and innovative technique to combat this problemof the design and manufacture of new drug molecule for specific diseases.[53] Molecular docking study provides an insight into the different types of intermolecular interactions between a target protein and its ligand in a three dimensional space; therefore, this method serves as a simple and alternative way in the process of designing, evaluating, and comparing new drugs.[54] Thus, in this article,an attempt has been made tostudy the binding affinities as well as protein-ligand interaction of nine nucleoside analogsagainst the main protease (6LU7) ofSARS-CoV-2.

Methods

Preparation of Protein

Crystal structures ofthemain protease (M^{pro}) of SARS-CoV-2 or COVID-19 with PDB ID: 6LU7wasretrieved through Protein Data Bank (http://www.rcsb.org/).In order to prepare the receptor protein input files, Graphical User Interface program "Auto Dock Tools (ADT) 1.5.6" from Molecular Graphics Laboratory developed by Scripps Research Institute wasused.[55] In a typical receptor protein preparation for docking study, input file was generatedby taking the specific chain of the protein (Chain A) and removing water molecules, ions, ligands, and subunits from the original structure file. The receptor protein input.pdbqt filewasprepared by addingpolar hydrogen atoms and Kollman united atom charges into the receptor PDB file.[56]

Preparation of Ligand

The three dimensional structure of the nucleoside analogs, includingTelbivudine (PubChem CID: 159269), Entecavir (PubChem CID: 135398508), Clevudine (PubChem CID: 73115), Zalcitabine (PubChem CID: 24066), Taribavirin (PubChem CID: 451448), Stavudine (PubChem CID: 18283), Lamivudine (PubChem CID: 60825), cordycepin (PubChem CID: 6303), and cordycepin triphosphate (PubChem CID: 65562), were downloaded in.sdf format from PubChem (http://pubchem.ncbi.nlm.nih.gov/) database and depicted in Figure 1. The 3D structures in.sdf format of nucleoside analogs were converted to standard.pdb file format using online SMILES translator (https://cactus.nci.nih.gov/translate/) and the input.pdbqt file was generated using ADT. Since the nucleoside analog drugswere non-peptides, Gasteiger charge was assigned and non-polar hydrogens were merged.

Docking Study

All docking simulations were performedin AutoDock Vina programme 1.1.2 developed by Scripps Research institute andresults of the docking study and intermolecular interactions between the receptors and nucleoside analogs were analyzed using BIOVIA Discovery Studio 2020 (DS) version 20.1.0.0 (Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016) and Edupymol version 1.7.4.4.[57,58] In a typical docking simulation, three dimensional affinity (grid) maps and electrostatic grid boxes of dimension 50×50×50 Å grid points and grid center (X, Y, Z) of −26.283, 12.599, and 58.966 with a spacing of 1.00 Åwere generated to cover the entire active site of the receptor protein. Lamarckian genetic algorithm and a standard protocol with default setting of other run parameters were used for the docking simula-

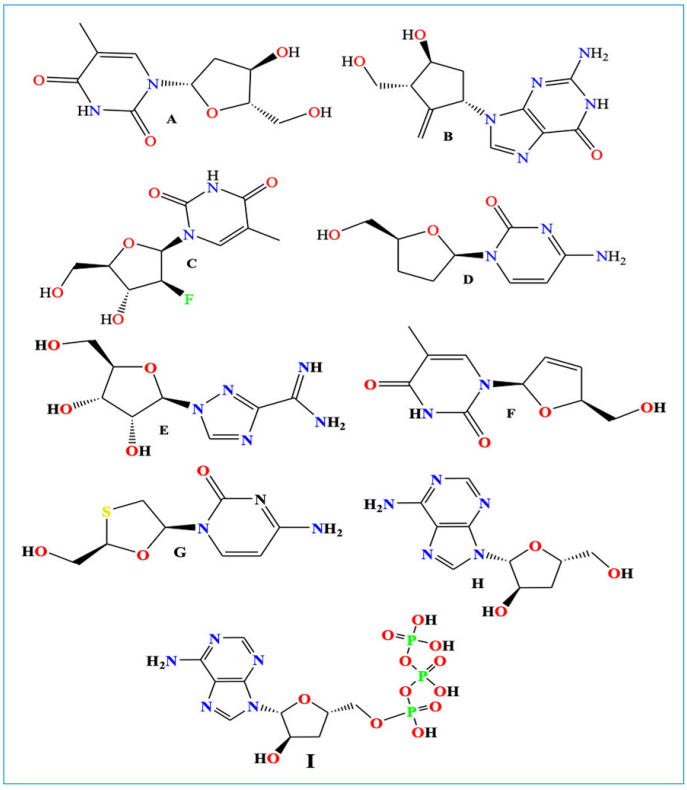

Figure 1. Structure ofthenucleoside analog antiviral drugs: **(a)** Telbivudine, **(b)** Entecavir, **(c)** Clevudine, **(d)** Zalcitabine, **(e)** Taribavirin, **(f)** Stavudine, **(g)** Lamivudine, **(h)** Cordycepin and **(I)** Cordycepintriphosphate.

tion. The predicted inhibitory constant (pKi) was calculated using the following standard ized equation.[59]

$pK_{i=10}$[Binding Energy Score /1.336]

Results and Discussion

According to WHO report, till 4th August 2020, a total number of 18,603,263 people have been infected with COVID-19 across the world and over 701253 people have lost their lives (Worldometer, Last updated: August 5th, 2020,https://www.worldometers.info/coronavirus). Till date, many countries are trying to develop a vaccine or antiviral drug forthe effective treatment ofCOVID-19.[5] However, many research studies have shown that the existing FDA approved drugs, such as Chloroquine, Hydroxychloroqunie (antimalarial drug), Leponavir, Ritonavir, Darunavir, Favipiravir (approved drug for HIV infection), Remdesivir, Ribavirin, Galidesivir (approved drug for Ebola virus infection), and Arbidol (influenza antiviral drug), are effective for the treatment of COVID-19.[6-11] Recent studies on SARS-CoV-2 have shown that the main protease (M^{pro}) is highly conserved across the coronavirus family and that they are mainly responsible for viral replication.[60] Moreover, the crystal structure of M^{pro} (6LU7) of SARS-CoV-2 in complex with the inhibitor ligand N3 have shown that the inhibitor ligand (N3) binds to the M^{pro} of SARS-CoV-2 through Cys145-His41catalytic dyad present at the interface between domain I and domain II on the active site of M^{pro} (6LU7), similar to SARS-CoV (Fig. 2).[61] There fore, the discovery of prominent and potentially active ther apeutic agents that could inhibit the M^{pro} is a dire need of the situation to combat the COVID-19 pandemic. Herein, in this research work, we studied the binding affinities and inhibitory potential of nine nucleoside analog antiviral agents against the main protease (6LU7) of SARS-CoV-2 through molecular docking simulation by taking the blind docking calculations i.e., covering the entire protein surface as the binding pocket in order to avoid sampling bias. The binding energies, types of interactions with possible target amino acid residues, and predicted inhibitory constant (pKi) are depicted in Table 1. The detailed analysis of binding affinity, intermolecular protein-ligand inter-

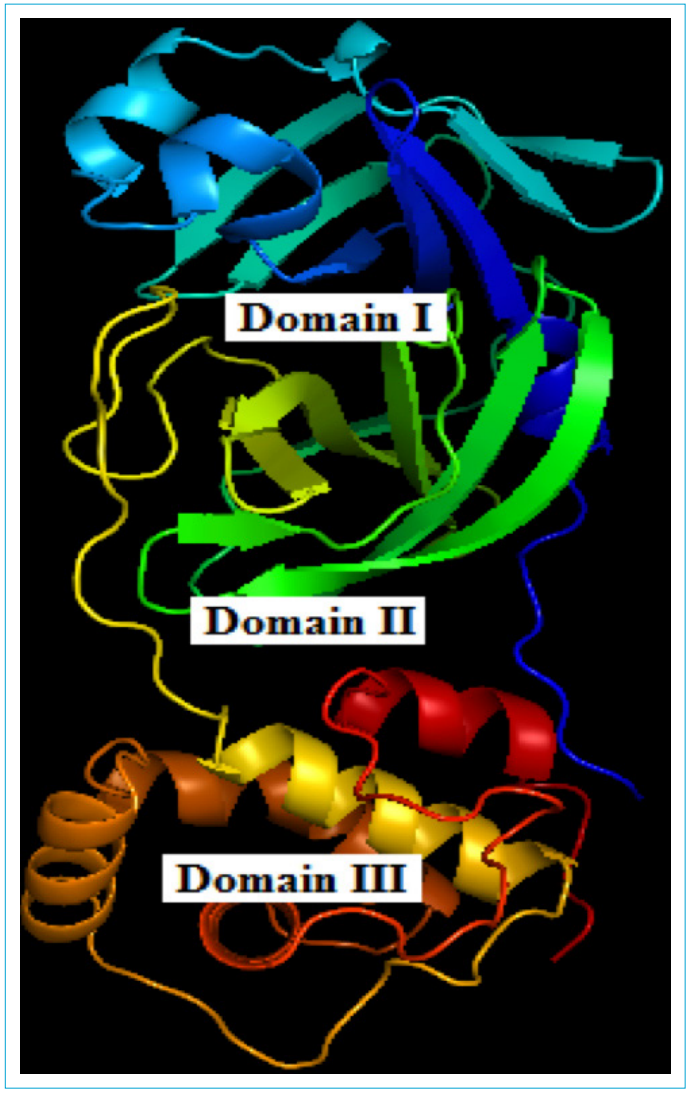

Figure 2. Structure of the M^{pro} of SARS-Cov-2 (Chain A) with domain I, II, and III.

Table 1. Summary of docking of nucleoside analog drugs against Main protease of SARS-CoV-2 (6LU7) with their respective binding energy (ΔG), predicted inhibitory constant (pKi), interacting amino acid residues and types of interactions

Nuceloside analogs:	Binding Energy (ΔG, Kcal/mole)	Predicted inhibitory constant (pKi) μM	Amino Acid residues	Types of interactions
Telbivudine	-6.5	7.7	Leu141, Gly143, Ser144, Cys145 and His163 His41 Met49, Phe140, Asn142, His164, Met165, Glu166 and His172	H-bonding Pi (π) donor H bond Van der walls
Entecavir	-6.8	6.1	Thr26, Leu141 and Glu166 Cys145 Thr25, leu27, His41, Met49, Phe140, Asn142, Gly143, Ser144, Met165, His172 and Gln189	H-bonding Pi(π)-alkyl Van der walls
Clevudine	-6.8	6.1	Phe140, Leu141, Ser144 and Cys145 His41 His164 Met49, Asn142, Gly143, His163, Met165, Glu166 and Gln189	H-bonding Pi(π)-sigma Halogen (F) bond Van der walls
Zalcitabine	-5.8	13.0	Leu141, Ser144, His163 and Glu166 Cys145 Phe140, Asn142, Gly143, His164, Met165, His172 and Gln189	H-bonding Pi(π)- alkyl Van der walls
Taribavirin	-6.1	10.4	Asn142, Ser144 and Glu166 Cys145 His41, Met49, Phe140, Leu141, Gly143, His163, his164, Met165, Asp187, Arg188 and Gln189	H-bonding Pi(π)- alkyl Van der walls
Stavudine	-6.5	7.7	Gly143, Ser144, Cys145 and His163 His41 and Cys145 Leu27, Met49, Phe140, Leu141, Asn142, His164, Met165, Glu166 and His172	H-bonding Pi(π)- alkyl Van der walls
Lamivudine	-5.7	14.0	Phe140, Ser144, Cys145, His163, His164 and Glu166 Cys145 Met49, His41, Leu141, Asn142, Gly143, Met165 and His172	H-bonding Pi(π)- alkyl Van der walls
Cordycepin	-6.5	7.7	Ser144 Cys145 Met165 His41 Leu141, Asn142, Gly143, his163, His164, Glu166, Asp187, Arg188 and Gln189	H-bonding Pi(π)- alkyl Pi(π)- Pi(π) T shaped Van der walls

Table 1. CONT.

Nuceloside analogs:	Binding Energy (ΔG, Kcal/mole)	Predicted inhibitory constant (pKi) μM	Amino Acid residues	Types of interactions
Cordycepin triphosphate	-6.9	5.7	His41, Cys145, Asp187 His41 Met49, Met165 Thr24. Thr25, Thr26, Leu27, Tyr54, Asn142, Gly143, Ser144, His163, His164, Glu166, Arg188, Gln189	H-bonding Pi(π)-Pi(π) T shaped Pi(π)-alkyl Van der walls

actions, and possible amino acid residue for each type of proteins with the studied ligand are given below:

Analysis of Docking Result

The docking results of all the nine nucleoside molecules against the main protease of SARS-CoV-2 show that drug molecules binds significantly with the target protein at the interface between domain I and domain II on the active site of M^{pro} (6LU7) of SARS-CoV-2. The interaction of Telbivudine with the main protease show that the molecule interacts with the protein 6LU7 through five hydrogen bonds, with a binding energy (ΔG)of–6.5 Kcal/mole (Fig. 3). These hydrogen bonds are formed between: C=O group of residue Leu141 and NH (3) proton of pyrimidine ring at a distance of 2.54Å; NH group of residue Gly143 and C=O (2) of pyrimidine ring at a distance of 2.25Å; NH group and OH group of residue Ser144 and C=O (2) and NH (3) group of pyrimide ring at a distanceof2.30Å and 2.21Å; NH2 and SH group of residue Cys145 and C=O (2) group of pyrimidine ring and O (1) atom of tetrahydrofuran ring at a distance of 2.20Å and 3.48Å; and NH(imidazole) group of residue His163 and C=O (4) of pyrimidine ring at a distance of 2.07Å. Other types of interactions such as π-donor hydrogen bonding between the residue His41 and Telbivudine and van der walls interactions between Telbivudine and residues Met49, Phe140, Asn142, His164, Met165, Glu166, and His172 have also been observed.

The docking of Entecavir with the main protease of SARS-CoV-2 have shown that the molecule interacts with the protein at the interface between domain I and domain II on the active site of the protein, with a binding energy (ΔG) of–6.8 Kcal/mole. The major interactions are characterized by three hydrogen bonds between: OH (4) group of cyclopentane ring of Entecavir and C=O group of residue Thr26 at a distanceof2.62Å; NH2(2) group of purine ring of Entecavir and C=O group of residue Leu141 at a distanceof2.00Å; and C=O (6) group of purine ring of Entecavir and residue Glu166 at a distanceof2.19Å (Fig. 4). Apart from the conventional hydrogen bonding, some π-alkyl (π-electron of

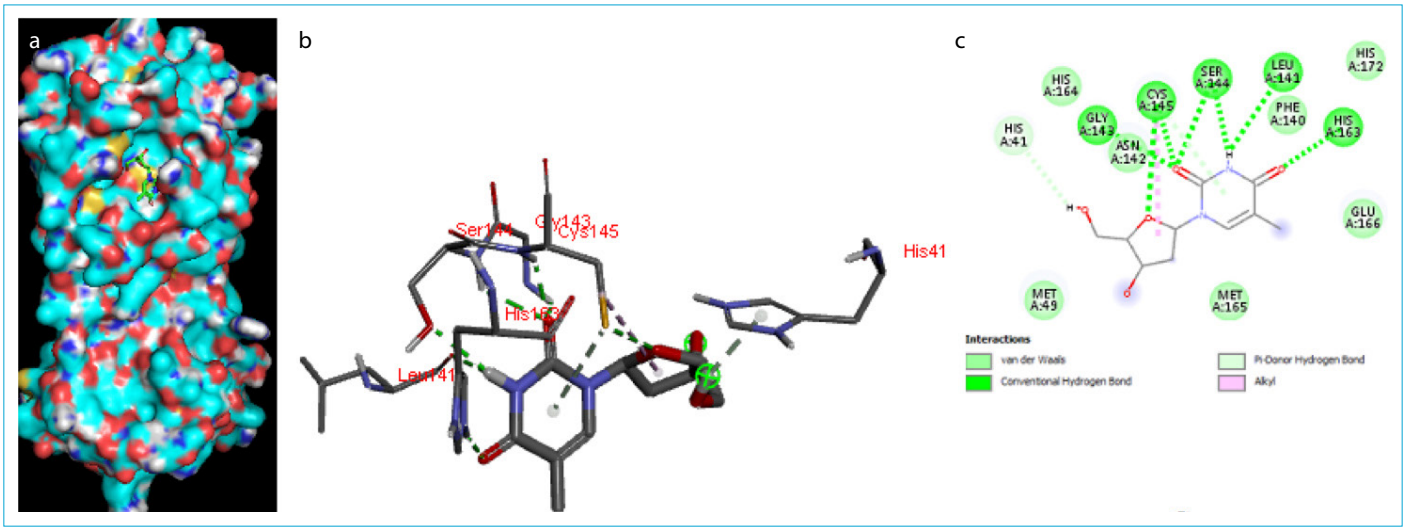

Figure 3. Telbivudine docked with M^{pro} (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Telbivudine in the pocket of protein (Telbivudine as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding) and **(c)** Binding interaction (2D) of Telbivudine with amino acid residues of protein 6LU7 (green dash line represents H-bonding).

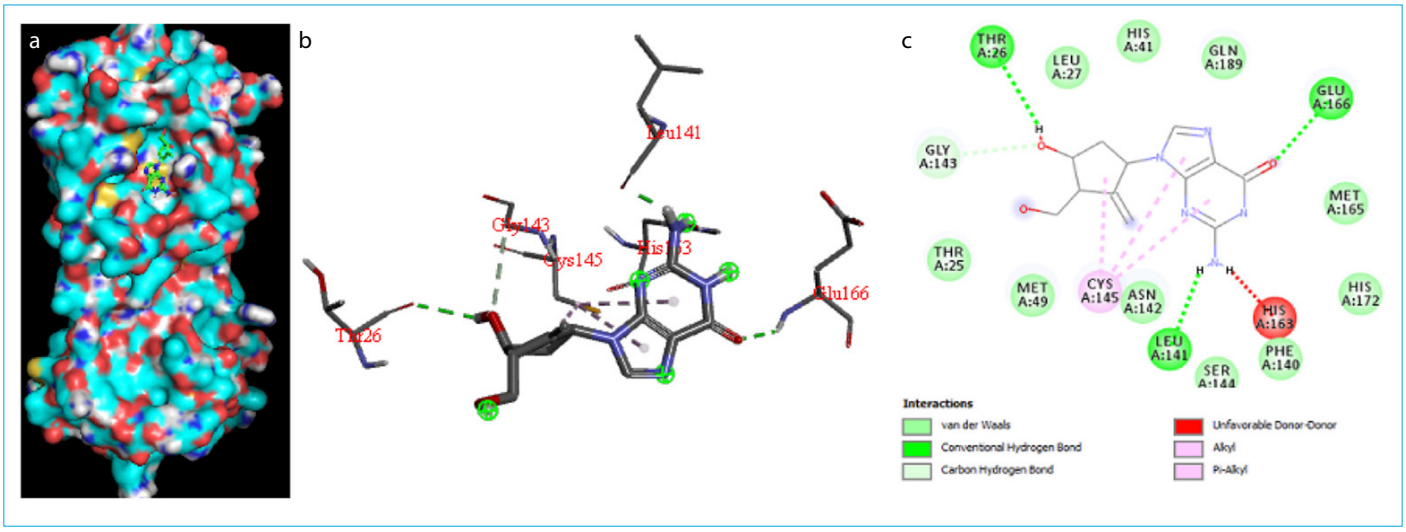

Figure 4. Entecavir docked with M^{pro} (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Entecavir in the pocket of protein (Entecavir as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding) and **(c)** Binding interaction (2D) of Entecvir with amino acid residues of protein 6LU7 (green dash line and red dash line represents H-bonding and unfavorable donor-donor interaction, respectively)

purine ring of Entecavir and alkyl group of residue Cys145) and van der walls interactions (between the drug Entecavir and residues Thr25, Leu27, His41, Met49, Phe140, Asn142, Gly143, Ser144, met165, his172, and Gln189) were observed. An unfavorable donor-donor interaction between the residue His163 and NH2 (2) of purine ring of Entecavir has also been found.

After the successful docking of Clevudine against the main protease of SARS-CoV-2, the result shows that Clevudine-fits inside the core pocket region at the interface between domain I and domain II on the active site of the protein, with a binding energy (ΔG)of–6.8 Kcal/mole. Clevudine interacts with the target protein by the formation of four prominent hydrogen bonds and these hydrogen bonds are formed between: C=O group of residue Phe140 and OH (4) group of tetrahydofuran ring of drug clevudine at a distance of 2.54Å; C=O group of residue Leu141 and H atom of CH2OH (5) group of clevudine at a distance of 2.31Å; NH2 and OH group of residue Ser144 and O and H atom of CH2OH (5) group of clevudine at a distance of 2.17Å and 2.48Å, respectively; and NH and SH group of Cys145 and O atom of CH2OH group and F (3) atom of tetrahydrofuran ring of clevudine at a distance of 2.54Å and 3.68Å, respectively (Fig. 5). Other types of interactions, such as π-sigma (between the π-electron of residue His41 and sigma electron of CH3 group of pyrimidine ring), Halogen (F) bond (between the F (3) atom of Clevudineand residue His163) and some van der walls interactions (between the residues Met49, Asn142, Gly143, His163, Met165, Glu166, and Gln189 and Clevudine) have also been observed.

Results obtained by the docking of Zalcitabine against the main protease of SARS-CoV-2 show the binding of Zalcitabine in the core pocket region at the interface between domain I and domain II of the main protease, with abinding affinity (ΔG)of–5.8 Kcal/mole. The major interaction between Zalcitabine and protein (6LU7) are characterized by four hydrogen bonds. The first two hydrogen bonds are formed by C=O group of residue Leu141 and OH group of residue Ser144 with NH2 group attached to pyrimidine ring of Zalcitabine at a distance of 2.22Å and 2.52Å, respectively. The other two hydrogen bonds are formed between NH (imidazole ring) of residue His163 and C=O(2) group attached to pyrimidine ring at a distance of 2.16Å and NH group of residue Glu166 and O(1) of tetrahydrofuran ring at a distance of 1.91Å (Fig. 6). The amino acid residue Cys145 was found to interact with Zalcitabine through π-alkyl interaction. Moreover, some van der walls interactions between Zalcitabine and residues Phe140, Asn142, Gly143, His164, Met165, His172, and Gln189 have been observed.

The results obtained by docking Taribavirin against themain protease of SARS-CoV-2 show that the drug molecule fits inside the core pocket region at the interface between domain I and domain II on the catalytically active site of main protein, with binding affinity (ΔG)of–6.1 Kcal/mole. Taribavirin forms three hydrogen bonds with the target protein. The first hydrogen bond exists between C=O group of residue Asn142 and OH (4) attached to tetrahydrofuran ring at a distance of 2.96Å. The second and third hydrogen bonds are formed by the NH group of residue Ser144 and NH group of residue Glu 166 with CH2OH (5) group and OH (3) group attached to tetrahydrofuran ring at a distance of 2.21Å and 2.26Å, respectively (Fig. 7). Apart fromthehy-

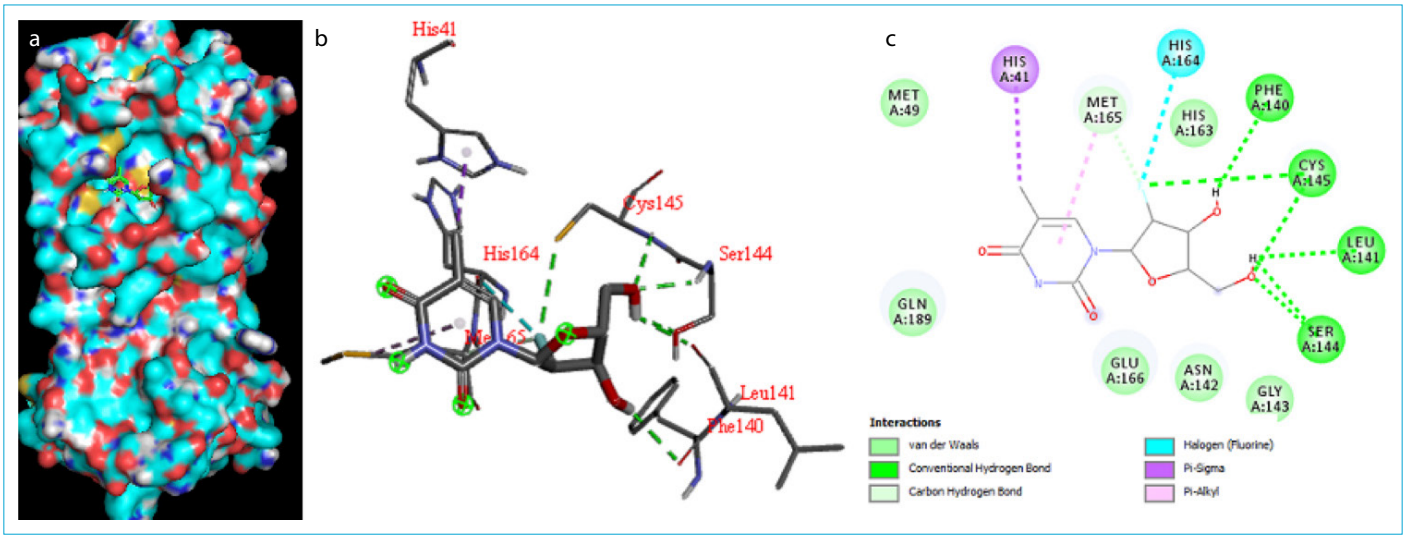

Figure 5. Clevudine docked with M^{pro} (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Clevudine in the pocket of protein (Clevudine as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding), and **(c)** Binding interaction (2D) of Clevudine with amino acid residues of protein 6LU7 (green dash, Purple dash, and blue dash line represents H-bond, Pi-sigma, and halogen bond, respectively)

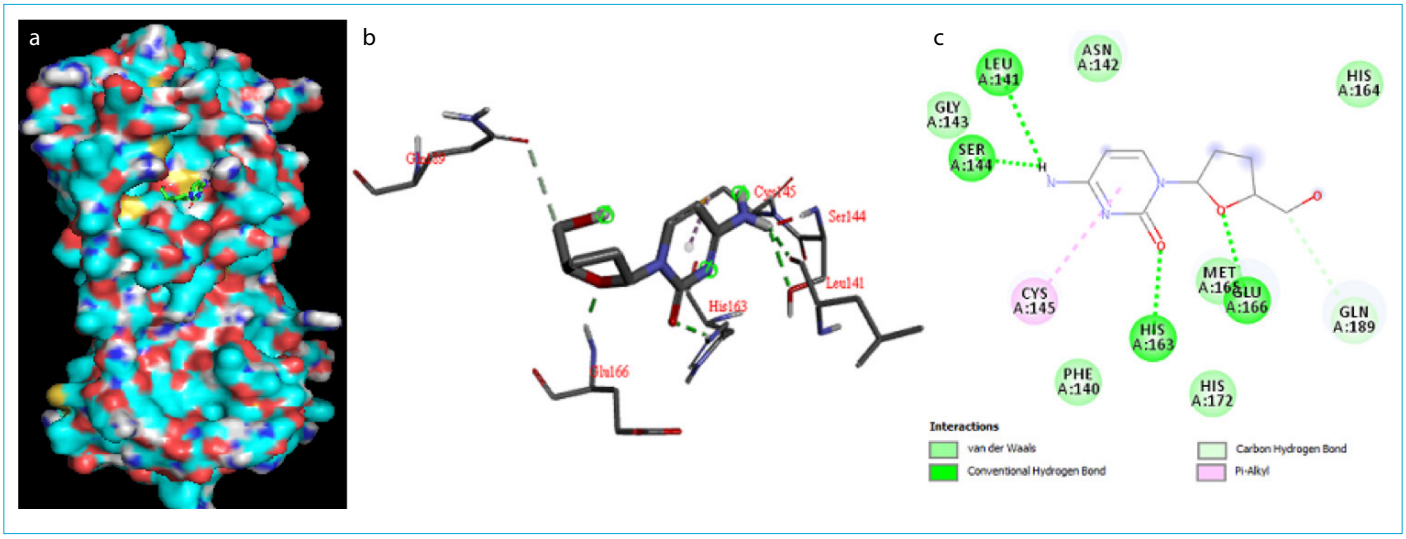

Figure 6. Zalcitabine docked with M^{pro} (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Zalcitabine in the pocket of protein (Zalcitabine as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding), and **(c)** Binding interaction (2D) of Zalcitabine with amino acid residues of protein 6LU7 (green dash and pink dash line represents H-bond and Pi-alkyl interaction, respectively)

drogen bonding interactions, π-alkyl (alkyl group of cys-145 and π-electron of triazole ring) interaction and some van der walls interaction between Taribavirin and residues His41, Met49, Phe140, Leu141, gly143, his163, His 164, Met165, Asp187, Arg188, and Gln189 were also observed.

The docking result of Stavudine against the main protease of SARS-CoV-2 showsthat Stavudine occupies the space at the interface between domain I and domain II on the catalytically active site ofthemain protease and interacts with the target protein by four major hydrogen bonding, with a binding energy (ΔG)of−6.5 Kcal/mole. Interestingly, the first three hydrogen bonds are formed by NH group of residues Gly143, Ser144, and Cys145 with C=O(2) group attached to the pyrimidine ring of Stavudine at a distance of 2.54Å, 2.12Å, and 2.34Å, respectively. The fourth hydrogen bonding exists between NH (imidazole ring) of residue His163 and C=O(4) group attached to pyrimidine ring at a distance of 2.07Å (Fig. 8). His41 and Cys145 forms π-alkyl interaction with the Stavudine molecule. The residues Leu27, Met49, Phe140, Leu141, Asn142, His164, Met165, Glu166, and His172 interact with Stavudine through van der Waals interactions.

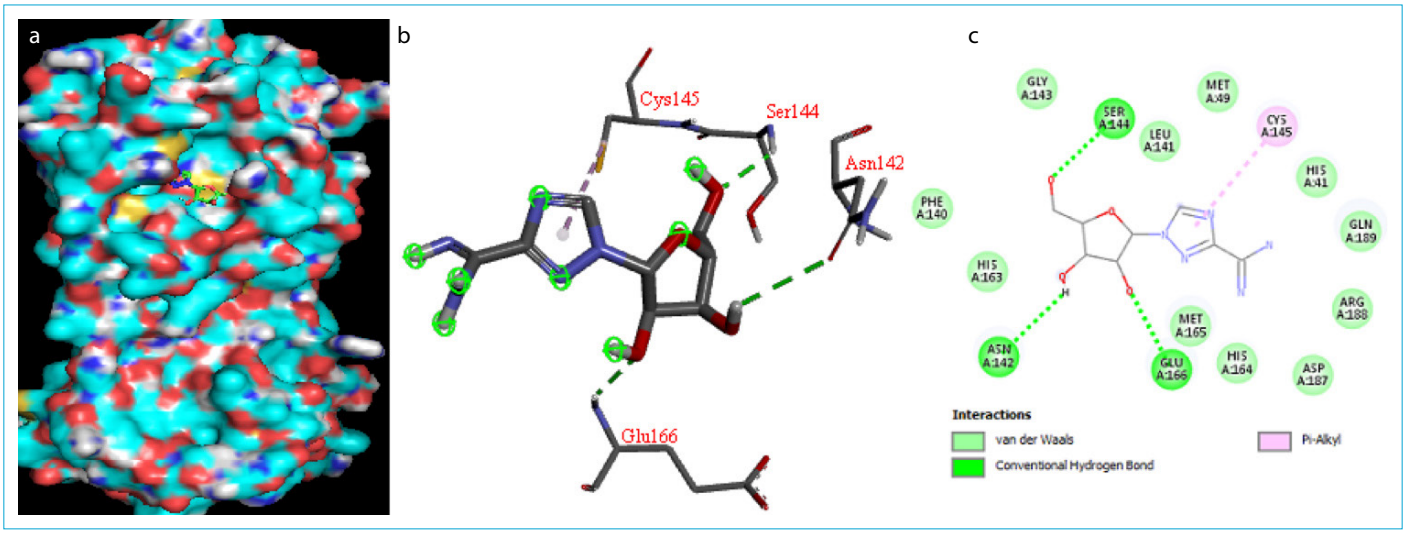

Figure 7. Taribavirin docked with M^{pro} (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Taribavirin in the pocket of protein (Taribavirin as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding), and **(c)** Binding interaction (2D) of Taribavirin with amino acid residues of protein 6LU7 (green dash and pink dash line represents H-bondand Pi-alkyl interaction, respectively).

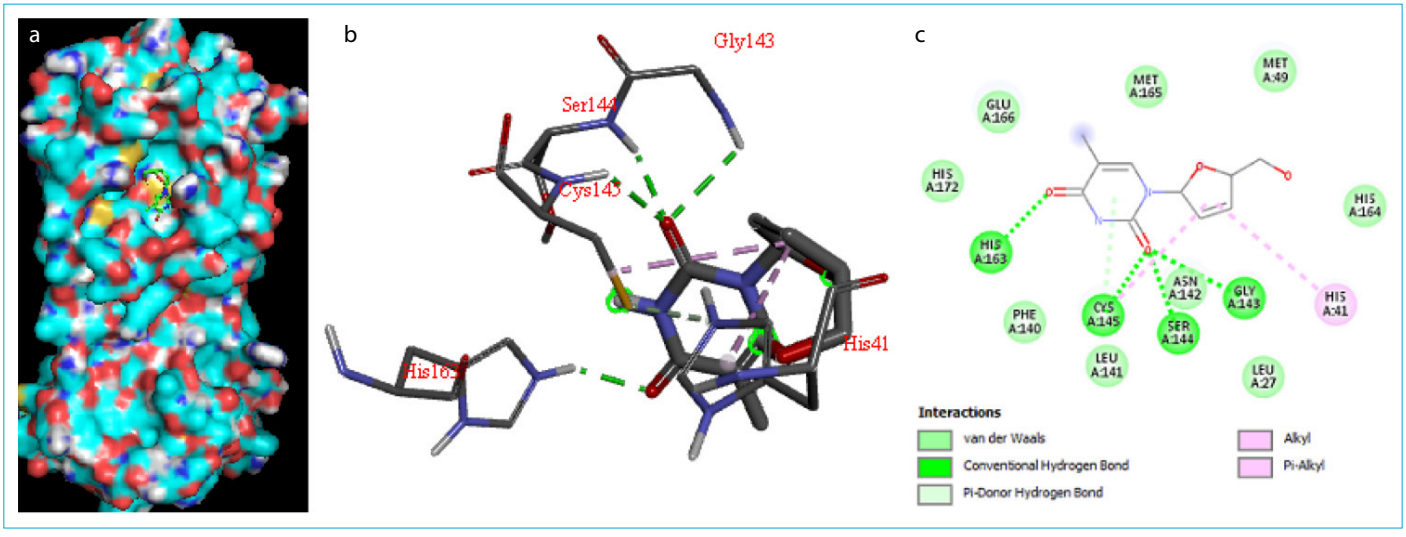

Figure 8. Stavudine docked with M^{pro} (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Stavudine in the pocket of protein (Stavudine as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding), and **(c)** Binding interaction (2D) of Stavudine with amino acid residues of protein 6LU7 (green dash and pink dash line represents H-bond and Pi-alkyl interaction, respectively).

Analysis of the docking result of Lamivudine with the main protease of SARS-CoV-2 revealed that Lamivudine interacts with the protein at the interface between domain I and domain II on the active catalytic side, with a binding affinity (ΔG) of–5.7 Kcal/mole. Seven major hydrogen bonding interactions exist between the protein and Lamivudine. These hydrogen bonding are found to exist between: C=O group of Phe140 and COOH group of residue Glu166 with NH2 (4) attached to pyrimidine ring of Lamivudine at a distance of 2.39Å and 2.65Å, respectively; NH2 group of Ser144 with C=O (2) group attached to pyrimidine ring at a distance of 2.73Å; NH2 and SH group of residue Cys145 with C=O (2) attached to pyrimidine ring and O(1) of tetrahydronfuran ring at a distance of 2.75Å, 3.23Å, and 3.35Å, respectively; NH (imidazole ring) of residue His163 with N(3) group of pyrimidine ring at a distance of 2.27Å; and C=O group of residue His164 with CH2OH group attached to tetrahydrofuran ring at a distance of 2.34Å (Fig. 9). Apart from these hydrogen bonding interactions, residue Cys145 interacts with the drug through π-alkyl interaction and residues His41, Met49, Leu141, Asn142, Gly143, Met165, and His172 interacts with Lamivudine through van der walls interactions.

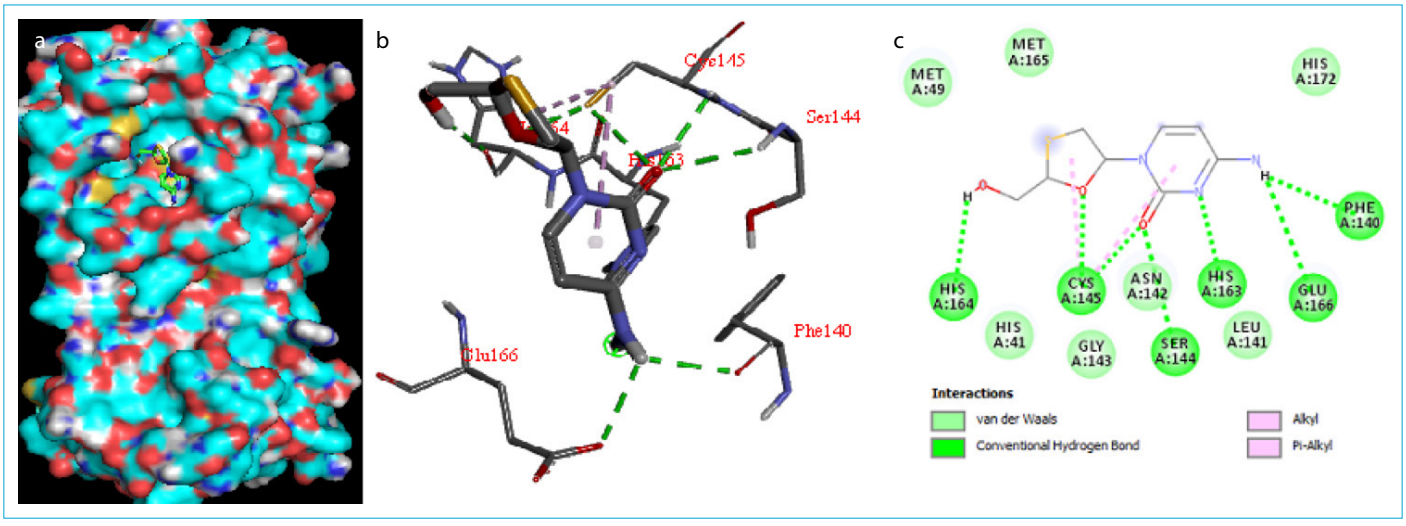

Figure 9. Lamivudine docked with Mpr° (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Lamivudine in the pocket of protein (Lamivudine as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding), and **(c)** Binding interaction (2D) of Lamivudine with amino acid residues of protein 6LU7 (green dash and pink dash line represents H-bond and Pi-alkyl interaction, respectively).

The docking of Cordycepin with the main protease of SARS-CoV-2 revealed that Cordycepin interacts with the protein in the core pocket region of catalytically active site (interface between domain I and domain II), with a binding affinity (ΔG) of–6.5Kcal/mole. Furthermore, NH2 and OH group of residues Ser144 and SH group residue Cys145 forms hydrogen bonds with CH2OH group attached to tetrahydrofuran ring at a distance of 2.17Å, 2.81Å, and 2.97Å, respectively (Fig. 10). Residue His41 forms π-π T shaped interactions with the π electron of purine ring and residue Met165 forms π-alkyl interaction. The amino acid residues Leu141, Asn142, Gly143, His163, His164, Glu166, Asp187, Arg188, and Gln189 interacts with Cordycepin through van der walls interactions.

The docking of Cordycepin triphosphate against the main protease of SARS-CoV-2 showed significant interactions with the receptor protein in the catalytic pocket of protein 6LU7, withabinding affinity (ΔG) of –6.9 Kcal/mole. Analysis of the docking of cordycepin triphosphate against protein 6LU7, the main protease ($M^{pr°}$) of SARS-COV-2, has shown that theyform favorable hydrogen bonding with the Cys145-His41 dyad of the main protease. Interestingly, NH (imidazole ring) of residue His41 forms hydrogen

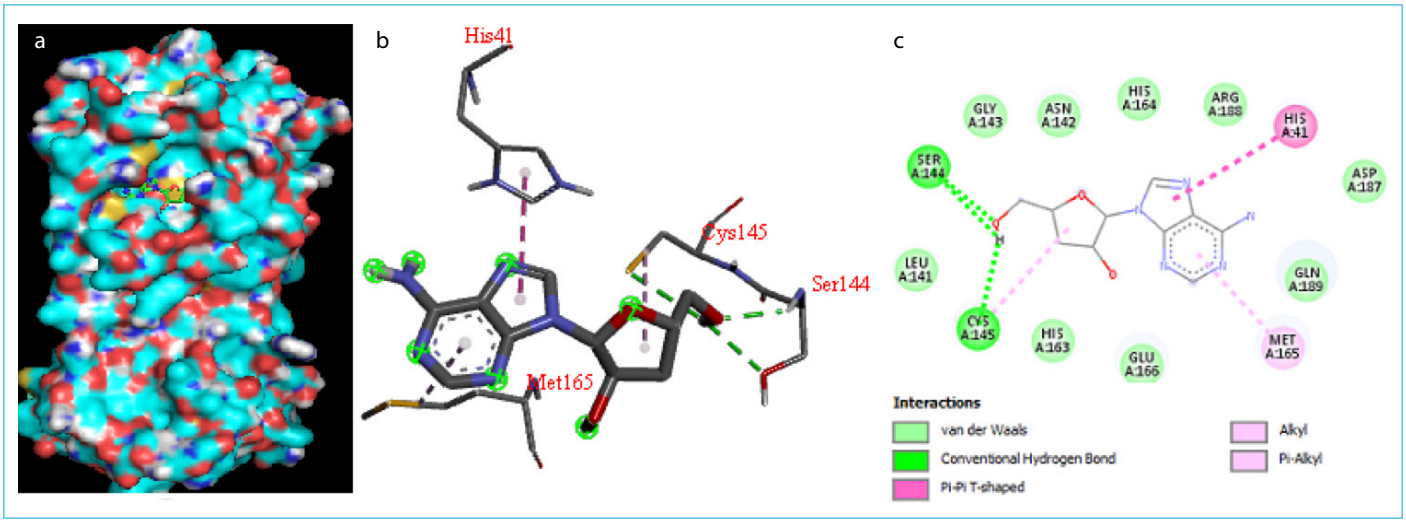

Figure 10. Cordycepin docked with $M^{pr°}$ (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Cordycepin in the pocket of protein (Cordycepin as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding), and **(c)** Binding interaction (2D) of Cordycepin with amino acid residues of protein 6LU7 (green dash, purple dash, and pink dash line represents H-bond, pi-pi T shaped. and Pi-alkyl interaction, respectively).

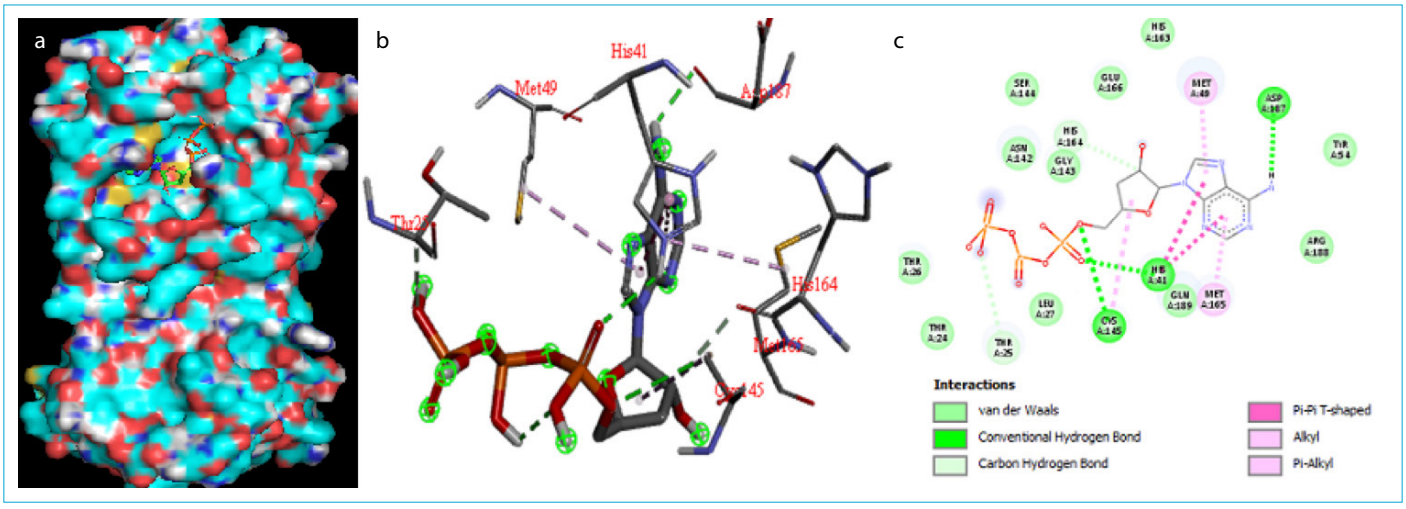

Figure 11. Cordycepin triphosphate docked with M^{pro} (6LU7) of SARS-CoV-2: **(a)** Best binding mode of Cordycepin triphosphate in the pocket of protein (Cordycepin triphosphate as green and red stick), **(b)** Amino acid residues involved in hydrogen bonding interaction (green dash line represents H-bonding), and **(c)** Binding interaction (2D) of Cordycepin triphosphate with amino acid residues of protein 6LU7 (green dash, purple dash, and pink dash line represents H-bond, Pi-Pi T shaped, and Pi-alkyl interaction, respectively).

bond with one of the oxygen atom of the phosphate linkage of cordycepin triphosphate at a distance of 2.45Å and SH group of residue Cys145 forms hydrogen bond with the oxygen atom at the phosphate (CH2O-P) linkage of the cordycepin triphosphate at a distance of 3.73Å. Also, there is another hydrogen bond interaction between carbonyl oxygen (C=O) of residue Asp187 and NH2(6) group of Purine moiety (Fig. 11) at a distance of 2.41Å. Apart from the conventional hydrogen bonding, Cordycepin triphosphate interacts with the protein 6LU7 through Pi (π)-Pi (π) T shaped interaction between residue His41 and pi (π) electron of purine ring at a distance of 4.24Å and 5.32Å, Pi (π)-alkyl (alkyl group of Met 49 and met165 with Pi (π)electron of purine ring) and van der walls interaction between the residues Thr24. Thr25, Thr26, Leu27, Tyr54, Asn142, Gly143, Ser144, His163, His164, Glu166, Arg188, and Gln189 and-Cordycepin triphosphate.

Conclusion

In this study, an attempt has been made to examine the inhibitory potential of nine nucleoside analogs against the main protease of SARS-COV-2. Based on the present study, it can be concluded thatthenine nucleoside analogs investigatedcan interact with the important amino acid residues of the studied proteins (6LU7) at the interface between domain I and domain II of the catalytically active site of SARS-COV-2 main protease and can inhibit the main protease ofthisnovel coronavirus. The docking studies suggest that the binding affinities (ΔG) of the nine nucleoside analogs against the main protease of SARS-CoV-2 are in the rangeof−5.7 Kcal/mole to −6.9 Kcal/mole andthatthe binding affinity of the nine nucleoside analogs follows the order:−6.9 Kcal/mole (cordycepin triphosphate)>−6.8 Kcal/mole (Entecavir≈ Clevudine)>−6.5 Kcal/mole (Telbivudine≈ Stavudine≈Cordycepin)>−6.1 Kcal/mole (Taribavirin)>−5.8 Kcal/mole (Zalcitabine)>−5.7 Kcal/mole (Lamivudine).Furthermore, *invitro* and *invivo* studies are required to transform these potential inhibitors as therapeutic agents in clinical trials.

Disclosures

Acknowledgements: Authors sincerely acknowledge the research facilities available at the St. Joseph's College, Darjeeling, India and Fr. Dr. Donatus Kujur SJ, Principal, St. Joseph's College, Darjeeling, India for his constant encouragement.

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – D.B., A.C.; Design – D.B.; Supervision – D.B.; Materials – A.C., D.B.; Data collection &/or processing – D.B., A.C.; Analysis and/or interpretation – A.C., D.B.; Literature search – D.B., A.C.; Writing – D.B., A.C.; Critical review – D.B., A.C.

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