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 rising concern about its fast spreading and capacity to transmit from human 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 (angiotensin-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 C and Sars-CoV-2 infection), Umifenovir (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 Ritonavir has been formulated as a therapeutic measure to manage the virulence to a great extent in COVID-19 patients (The Scientist, February 3 2020,
https://www.the-scientist.com/news-opinion/flu-and-anti-hiv-drugs-show-efficacy-against-coronavirus-67052). However, these antiviral or antimalarial drugs have some limitations for the treatment of COVID-19. Moreover, so far, there is no specific drug against COVID-19 approved by the US Food and Drug Administration Agency.[12,13] Therefore, 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 outbreak of COVID-19, different research groups have been continuously working in designing and formulating antiviral drugs and vaccines 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 SARS-CoV-2. Moreover, the nucleoside analogs usually show antiviral activities by inhibiting the viral replication through the blockage 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 inhibitor), 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 the treatment of many viral diseases.[42-52] In recent times, bioinformatics have provided an alternative and innovative technique to combat this problem of 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 to study the binding affinities as well as protein-ligand interaction of nine nucleoside analogs against the main protease (6LU7) of SARS-CoV-2.

Methods

Preparation of Protein

Crystal structures of the main protease (Mpro) of SARS-CoV-2 or COVID-19 with PDB ID: 6LU7 were retrieved 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 was used.[55] In a typical receptor protein preparation for docking study, input file was generated by 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 file was prepared by adding polar hydrogen atoms and Kollman united atom charges into the receptor PDB file.[56]

Preparation of Ligand

The three-dimensional structure of the nucleoside analogs, including Telbivudine (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 drugs were non-peptides, Gasteiger charge was assigned and non-polar hydrogens were merged.

Docking Study

All docking simulations were performed in AutoDock Vina programme 1.1.2 developed by Scripps Research institute and results 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 Modelling 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 50x50x50 Å grid points and grid center (X, Y, Z) of −26.283, 12.599, and 58.966 with a spacing of 1.00 Å were 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-
The predicted inhibitory constant (pKi) was calculated using the following standardized equation.\(^{[59]}\)

\[
pKi = 10 \left( \frac{\text{Binding Energy Score}}{1.336} \right)
\]

Results and Discussion

According to WHO report, till 4\(^{th}\) August 2020, a total number of 18,603,263 people have been infected with COVID-19 across the world and over 701,253 people have lost their lives (Worldometer, Last updated: August 5\(^{th}\), 2020, https://www.worldometers.info/coronavirus). Till date, many countries are trying to develop a vaccine or antiviral drug for the effective treatment of COVID-19.\(^{[5]}\) However, many research studies have shown that the existing FDA approved drugs, such as Chloroquine, Hydroxychloroquine (antimalarial drug), Lopinavir, 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\(^{\text{pre}}\)) is highly conserved across the coronavirus family and that they are mainly responsible for viral replication.\(^{[60]}\) Moreover, the crystal structure of M\(^{\text{pre}}\) (6LU7) of SARS-CoV-2 in complex with the inhibitor ligand N3 have shown that the inhibitor ligand (N3) binds to the M\(^{\text{pre}}\) of SARS-CoV-2 through Cys145-His41 catalytic dyad present at the interface between domain I and domain II on the active site of M\(^{\text{pre}}\) (6LU7), similar to SARS-CoV (Fig. 2).\(^{[61]}\)

Therefore, the discovery of prominent and potentially active therapeutic agents that could inhibit the M\(^{\text{pre}}\) 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 interaction.
| Nucleoside 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 | H-bonding            |
|                     |                               |                                      | His41               | Pi (n) donor H bond   |
|                     |                               |                                      | Met49, Phe140, Asn142, His164, Met165, Glu166 and His172 | Van der walls       |
| Entecavir           | -6.8                          | 6.1                                  | Thr26, Leu141 and Glu166 Cys145 | H-bonding            |
|                     |                               |                                      | Thr25, Leu27, His41, Met49, Phe140, Asn142, Gly143, Ser144, Met165, His172 and Gln189 | Van der walls       |
|                     |                               |                                      | Cys145 Thr25, His41, Met49, Phe140, Asn142, Gly143, Ser144, Met165, His172 and Gln189 | Pi(n)-alkyl          |
|                     |                               |                                      | Gly143, Phe140, Asn142, Gly143, His163, Met165, Glu166 and Gln189 | Van der walls       |
| Clevudine           | -6.8                          | 6.1                                  | Phe140, Leu141, Ser144 and Cys145 | H-bonding            |
|                     |                               |                                      | Cys145              | Pi(n)-sigma          |
|                     |                               |                                      | His41               | Halogen (F) bond     |
|                     |                               |                                      | Met49, Asn142, Gly143, His163, Met165, Glu166 and Gln189 | Van der walls       |
|                     |                               |                                      | Phe140, Asn142, Gly143, His163, Met165, Glu166 and Gln189 | Van der walls       |
| Zalcitabine         | -5.8                          | 13.0                                 | Leu141, Ser144, His163 and Glu166 Cys145 | H-bonding            |
|                     |                               |                                      | Phe140, Asn142, Gly143, His163, Met165, Glu166 and Gln189 | Pi(n)-alkyl          |
|                     |                               |                                      | His164              | Van der walls       |
|                     |                               |                                      | Met49, Asn142, Gly143, His163, Met165, Glu166 and Gln189 | Van der walls       |
| Taribavirin         | -6.1                          | 10.4                                 | Asn142, Ser144 and Glu166 Cys145 | H-bonding            |
|                     |                               |                                      | Asn142, Ser144 and Glu166 Cys145 | Pi(n)-alkyl          |
|                     |                               |                                      | Leu141, Gly143, His163, His164, Met165, Asp187, Arg188 and Gln189 | Van der walls       |
|                     |                               |                                      | Leu141, Gly143, His163, His164, Met165, Asp187, Arg188 and Gln189 | Van der walls       |
| Stavudine           | -6.5                          | 7.7                                  | Gly143, Ser144, Cys145 and His163 | H-bonding            |
|                     |                               |                                      | Gly143, Ser144, Cys145 and His163 | Pi(n)-alkyl          |
|                     |                               |                                      | His41 and Cys145    | Van der walls       |
|                     |                               |                                      | Leu27, Met49, Phe140, Leu141, Asn142, His164, Met165, Glu166 and His172 | Van der walls       |
| Lamivudine          | -5.7                          | 14.0                                 | Phe140, Ser144, Cys145, His163, His164 and Glu166 Cys145 | H-bonding            |
|                     |                               |                                      | Phe140, Ser144, Cys145, His163, His164 and Glu166 Cys145 | Pi(n)-alkyl          |
|                     |                               |                                      | Met49, His41, Leu141, Cys145 Met49, His41, Leu141, Asn142, Gly143, Met165 and His172 | Van der walls       |
|                     |                               |                                      | Cys145 Cys145 Met49, His41, Leu141, Asn142, Gly143, Met165 and His172 | Van der walls       |
| Cordycepin          | -6.5                          | 7.7                                  | Ser144 Cys145 Met165 His41 | H-bonding            |
|                     |                               |                                      | Ser144 Cys145 Met165 His41 | Pi(n)-alkyl          |
|                     |                               |                                      | Leu141, Asn142, Gly143, His163, His164, Glu166, Asp187, Arg188 and Gln189 | 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 $M^{\text{pro}}$ (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 ($\Delta G$) 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 distance of 2.30Å 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 $\pi$-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 ($\Delta G$) 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 distanceof 2.62Å; NH2(2) group of purine ring of Entecavir and C=O group of residue Ser144 at a distanceof 2.00Å; and C=O (6) group of purine ring of Entecavir and residue Glu166 at a distanceof 2.19Å (Fig. 4). Apart from the conventional hydrogen bonding, some $\pi$-alkyl ($\pi$-electron of

![Figure 3. Telbivudine docked with $M^{\text{pro}}$ (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).](image-url)
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/mol. 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 tetrahydrofuran ring of drug clevudine at a distance of 2.54Å; C=O group of residue Leu141 and H atom of CH2OH (5) group of cleavage at a distance of 2.31Å; NH2 and OH group of residue Ser144 and O and H atom of CH2OH (5) group of cleavage 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 cleavage 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 Clevudine and residue His163) and some van der walls interactions (between the residues Met49, Asn142, Gly143, His163, Met165, 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 a binding affinity (ΔG) of −5.8 Kcal/mol. The major interaction between Zalcitabine and protein (6LU7) is characterized by four hydrogen bonds. The first two hydrogen bonds are formed between NH (imidazole ring) of residue His163 and C=O(2) group attached to pyrimidine ring of Zalcitabine 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 the main 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/mol. Taribavirin forms three hydrogen bonds with the target protein. The first hydrogen bond exists between C=O group of residue Asn142 and OH (4) group 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 Glu166 with CH2OH (5) group and OH (3) group attached to tetrahydrofuran ring at a distance of 2.21Å and 2.26Å, respectively (Fig. 7).
drogen bonding interactions, π-alkyl (alkyl group of cysteine 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 of the enzyme 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.
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 tetrahydrofuran 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.
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 ($\Delta G$) of $-6.5$ Kcal/mole. Furthermore, NH$_2$ and OH group of residues Ser144 and SH group residue Cys145 forms hydrogen bonds with CH$_2$OH group attached to tetrahydrofuran ring at a distance of 2.17Å, 2.81Å, and 2.97Å, respectively (Fig. 10). Residue His41 forms $\pi$-$\pi$ T shaped interactions with the $\pi$ electron of purine ring and residue Met165 forms $\pi$-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, with a binding affinity ($\Delta G$) of $-6.9$ Kcal/mole. Analysis of the docking of cordycepin triphosphate against protein 6LU7, the main protease (Mpr°) of SARS-COV-2, has shown that they form favorable hydrogen bonding with the Cys145-His41 dyad of the main protease. Interestingly, NH (imidazole ring) of residue His41 forms hydrogen bonds with the Cys145-His41 dyad of the main protease.

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).

Figure 10. Cordycepin docked with Mpr° (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).
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 that the nucleoside analogs investigated can 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 of this novel 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 range of −5.7 Kcal/mole to −6.9 Kcal/mole and the 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, *in vitro* and *in vivo* studies are required to transform these potential inhibitors as therapeutic agents in clinical trials.

**Disclosures**

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