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Sofosbuvir can inhibit the newly emerged coronavirus (2019-nCoV) in Wuhan, China

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Abstract:	A newly emerged Human Coronavirus (HCoV) is reported last month in Wuhan, China (2019-nCoV). Until today three deaths and more than 200 confirmed cases reported in China, Thailand, and Japan. HCoVs are zoonotic viruses that transmit from animals to humans through direct contact. Six different strains of HCoV were reported, during the last century, which has a different pathogenic burden and spread potentials. The two most famous strains of HCoVs that have significant health complications are the Severe Acute Respiratory Syndrome coronavirus (SARS CoV) and the Middle East Respiratory Syndrome coronavirus (MERS CoV). Based on the World Health Organization (WHO) reports, SARS HCoV is responsible for more than 8000 cases with confirmed 774 deaths. Additionally, MERS HCoV is responsible for 858 deaths out of about 2500 reported cases. In this study, the newly emerged Wuhan HCoV is targeted by anti-polymerase drugs including the approved Sofosbuvir and Ribavirin. Sequence analysis, modeling and docking are used to build a model for Wuhan 2019-nCoV RNA dependent RNA polymerase (RdRp). The results suggest the effectiveness of Sofosbuvir, IDX-184 and Ribavirin as a potent drug against the newly emerged HCoV disease.

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Short running title:

DAA against the RdRp of 2019-nCoV

Abstract

A newly emerged Human Coronavirus (HCoV) is reported last month in Wuhan, China (2019-nCoV). Until today three deaths and more than 200 confirmed cases reported in China, Thailand, and Japan. HCoVs are zoonotic viruses that transmit from animals to humans through direct contact. Six different strains of HCoV were reported, during the last century, which has a different pathogenic burden and spread potentials. The two most famous strains of HCoVs that have significant health complications are the Severe Acute Respiratory Syndrome coronavirus (SARS CoV) and the Middle East Respiratory Syndrome coronavirus (MERS CoV). Based on the World Health Organization (WHO) reports, SARS HCoV is responsible for more than 8000 cases with confirmed 774 deaths. Additionally, MERS HCoV is responsible for 858 deaths out of about 2500 reported cases. In this study, the newly emerged Wuhan HCoV is targeted by anti-polymerase drugs including the approved Sofosbuvir and Ribavirin. Sequence analysis, modeling and docking are used to build a model for Wuhan 2019-nCoV RNA dependent RNA polymerase (RdRp). The results suggest the effectiveness of Sofosbuvir, IDX-184 and Ribavirin as a potent drug against the newly emerged HCoV disease.

Keywords

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Introduction

A New emerged human coronavirus (2019-nCoV) is reported in December 2019 in Wuhan, China [1,2]. According to the World Health Organization (WHO) surveillance draft in January 2020, any traveler to Wuhan, Hubei Province in China, two weeks before the onset of the symptoms, is suspected to be a 2019-nCoV patient [2,3]. Additionally, WHO distributed interim guidance for laboratories that carry out the testing for the newly emerged outbreak and infection prevention and control guidance [4,5]. 2019-nCoV viral pneumonia is related to the seafood market when an unknown animal is responsible for the emergence of the outbreak [1]. Other countries started their surveillance borders to prevent the spread of the new unknown coronavirus [6]. Until two weeks ago, 41 cases are confirmed to be 2019-nCoV positives leaving one dead and seven in critical care. This number is grossly increasing every day and the number of confirmed cases at the date of writing this manuscript is 217 and 3 deaths [7]. On 20 January 2020, the National Health Commission of China confirmed the human-to-human transmission of the Wuhan outbreak (2019-nCoV) [7]. The symptoms include fever, malaise, dry cough, shortness of breath and respiratory distress [1].

2019-nCoV is a member of *Betacoronaviruses* like the Severe Acute Respiratory Syndrome Human coronavirus (SARS HCoV) and the Middle-East Respiratory Syndrome Human coronavirus (MERS HCoV) [8,9]. Until today, six different strains of Human coronaviruses (HCoVs) have been reported, in addition to the newly emerged 2019-nCoV [1,10]. 229E and NL63 strains of HCoVs belong to *Alphacoronaviruses* while OC43, HKU1, SARS, MERS, and 2019-nCoV HCoVs belong to *Betacoronaviruses* [1,8]. SARS and MERS HCoV are the most aggressive strains of coronaviruses, leaving about 800 deaths each. SARS HCoV has a 10% mortality rate, while MERS HCoV has a 36% mortality rate, according to the WHO [8,10-13].

HCoVs generally are positive-sense and very long (30,000 bp) single-stranded RNA viruses. Two groups of protein characterize HCoVs; structural, such as Spike (S), Nucleocapsid (N) Matrix (M) and Envelope (E), and non-structural proteins such as RNA dependent RNA polymerase (RdRp) (nsp12) [8]. RdRp is a crucial enzyme in the life cycle of RNA viruses, including coronaviruses. RdRp is targeted in different RNA viruses, including Hepatitis C Virus (HCV), Zika Virus (ZIKV), and coronaviruses (CoVs) [14-22]. The active site of RdRp is highly conserved representing two successive aspartate residues protruding from a beta-turn structure making them surface accessible through the nucleotide channel (free nucleotides can pass through) [23,24].

In this study, the 2019-nCoV RdRp model is built using homology modeling after sequence comparison to the available structures in the protein data bank [25]. After model validation, molecular docking is performed to test some direct acting antiviral (DAA) drugs against 2019-nCoV RdRp. The results are promising and suggest possible inhibition for the currently available therapeutics against the newly emerged coronavirus.

Materials and methods

Sequence alignment and modeling

The only available gene for the newly emerged 2019-nCoV (NC_045512.2) is retrieved from the National Center for Biotechnology Information (NCBI) nucleotide database [26]. Swiss Model web server is used to build a model for RdRp using its automated mode [27]. SARS HCoV solved structure (PDB ID: 6NUR, chain A) is used as a template that shares identical 97.08 % of the sequence with 2019-nCoV RdRp. 6NUR, chain A, is a SARS HCoV non-structural protein

12 (nsp12) solved experimentally using cryo-Electron Microscopy (cryo-EM) with 3.1 Å resolution deposited in the protein data bank last year [28]. The Molprobity web server of the Duke University, and the structure analysis and verification server (SAVES) of the University of California Los Angles (UCLA) are used to test the model [29,30]. The program used to judge the validity of the model are PROCHECK [31], Verify 3D [32], PROVE [33], and ERRAT [34] in addition to the Ramachandran plot of the Molprobity. After validation, the computational chemistry workspace SCIGRESS is used to minimize the model and to perform molecular docking experiments [14,21,35,36]. The minimization of the model is performed using the MM3 force field after the addition of missed Hydrogen atoms [37].

Molecular Docking

Docking experiment is performed using the optimized 2019-nCoV and SARS (PDB ID: 6NUR, chain A) RdRps by the aid of AutoDock Vina software implemented in SCIGRESS [38]. Five different compounds are tested against Wuhan 2019-nCoV RdRp, including Sofosbuvir, IDX-184, Ribavirin, Guanosine triphosphate (GTP), and Uracil triphosphate (UTP). Sofosbuvir is an approved drug by the Food and Drugs Administration (FDA) against Hepatitis C Virus (HCV) Non-structural protein 5 (NS5B) RdRp in the year 2013 [18,39-41]. It gives excellent results against other viruses including the Zika virus [19,22,42,43]. IDX-184 was under clinical trials against HCV and gave better results compared to other drugs against HCV, MERS and SARS HCoVs, and Zika virus RdRps [8,17,18,44-47]. Ribavirin is a broad-acting antiviral drug used to treat different viruses in combination with immunomodulators or direct-acting antivirals [48-50].

After docking, the structures are examined by the aid of the Protein-Ligand Interaction Profiler (PLIP) web server (Technical University of Dresden) and tabulated for comparison [51].

Results and discussion

2019-nCoV RdRp modeling

Figure 1A shows the multiple sequence alignment (MSA) of RNA dependent RNA polymerases from Different HCoV strains including the *Alphacoronaviruses* (229E and NL63) and the *Betacoronaviruses* (OC43, HKU1, SARS, MERS, and 2019-nCoV). SARS HCoV secondary structure is shown at the top of the MSA (PDB ID: 6NUR chain: A) while its water accessibility found at the bottom of the MSA. Highly accessible residues are in blue boxes while buried residues are represented in white at the bottom of the MSA. The black-dashed rectangle marks active site residues (successive aspartates residues D255 and D256). The active site aspartates are protruding from the beta-turn joining the β15 and β16. As implied from the MSA, the active site is highly conserved (highlighted in red). Also, the 5Å region surrounding the D255 and D256 is highly conserved in all HCoVs, as shown by the blue-dashed rectangles. This region includes Y114, C117, N186, N190, M251, I252, L253, S254, A257, V258, E306, F307, C308, and S309. The active site residues and most of the 5Å region surrounding it are surface accessible, can bind to the free nucleotides (ATP, GTP, CTP, and UTP) [17,23].

Figure 1B shows the structure of the Wuhan 2019-nCoV RdRp model in the green ribbon (right) and green surface (left) representations. Active site residues D255 and D256 are in red for clarification (see the enlarged panel at the center of the figure). The active site is surface accessible as we can see from the surface representation allowing the interaction with the free nucleotides passing through the nucleotide channel of the RdRp.

For Wuhan 2019-nCoV the percent sequence identity against SARS, MERS, OC43, NL63, 229E, and HKU1 HCoV strains are 90.18%, 56.76%, 55.07%, 48.79%, 48.55%, and

48.16%, respectively. Therefore, the SARS HCoV is the closest strain to the 2019-nCoV. The complete genome for Wuhan SARS-like HCoV has a sequence identity of 89.12 % and 82.34% with Bat SARS-like coronavirus isolate *bat-SL-CoVZC45* and SARS coronavirus *ZS-C*, respectively. This information is important for drug designers to find a quick and potent solution against the newly emerged 2019-nCoV strain.

Wuhan 2019-nCoV RdRp model (801 residues) is built by the aid of the automated homology modeling, Swiss Model, web server using SARS HCoV RdRp (PDB ID: 6NUR, chain A) as a homolog. The model has a very high (97.08%) sequence identity to the template suggesting the high-quality model that could be obtained. The model is valid based on the values we obtain from the validation web servers. The Ramachandran plot shows 100% of the residues in the allowed regions, 97.5% in the most favored region. Additionally, 89.9% of the residues have averaged 3D-1D score $\geq$ 0.2 based on the Verify 3D software, while the overall quality factor of ERRAT is 95.9%.

DAA binding to 2019-nCoV RdRp

Before performing the docking study, the structures of the small molecules (GTP, UTP, Sofosbuvir, IDX-184, and Ribavirin) are prepared, ensured to be in the optimized triphosphate form. Optimization is performed using MM3 then PM6 force field after that further optimization is accomplished through B3LYP functional of Density Functional Theory (DFT) quantum mechanics [37,52-54]. The active site aspartates D255 and D256 are treated as flexible during the docking experiment. A grid box size of 30 × 30 × 30 Å centered at (x, y, z) of (142.1, 138.7, 150.0) Å is used in the docking by utilizing the AutoDock tools [55]. AutoDock Vina utilizes its scoring function (Vina) to predict the interaction between the abovementioned ligands and the RdRps' active site. Figure 2 shows the docking score values for 2019-nCoV (blue columns) and

SARS HCoVs (orange columns). The SARS solved structure (PDB ID: 6NUR, chain A) is used to dock the same ligands in order to compare its binding energy to that of 2019-nCoV RdRp. The grid box (30 × 30 × 30 Å) for SARS RdRp is centered at (141.2, 138.5, 149.4) Å. As reflected from the docking scores, the five compounds, including the physiological GTP and UTP and the three drugs IDX-184, Sofosbuvir, and Ribavirin, can bind to both 2019-nCoV and SARS HCoV RdRps with good binding energy (-6.5 up to -9.0 kcal/mol). Despite SARS HCoV RdRp show slightly higher binding energies (lower in binding) compared to 2019-nCoV RdRp, the difference is still non-significant for Ribavirin, Sofosbuvir and its parent nucleotide, UTP. On average, 0.93 kcal/mol is the difference between the SARS and 2019-nCoV RdRps' binding energies for these compounds. On the other hand, the difference between 2019-nCoV and SARS HCoV RdRps' binding energies to IDX-184 and its parent nucleotide GTP are 2.3 and 1.6 kcal/mol, respectively. Additionally, all the tested compounds show lower (better) binding energies to 2019-nCoV RdRp compared to SARS RdRp.

In order to check the possible reason for the differences in the binding energies, we examined the interaction complexes formed after docking by the aid of the PLIP web server. Figure 3 shows the formed interactions between the DAA drugs and 2019-nCoV RdRp after docking. The docking scores are listed under each complex to reflect the binding potency. Ligands are shown in orange sticks while protein residues are in cyan stick representations labeled with its one-letter code. H-bonds are solid blue lines while the dashed lines represent the hydrophobic interactions. Only one salt bridge (yellow spheres connected by a dashed line) is formed in the case of IDX-184 with D514 which is responsible for the increased stabilization of the formed complex, reflected on the docking score. The number of H-bonds for IDX-184, Sofosbuvir and Ribavirin are 11, 7, and 13, respectively. On the other hand, IDX-184 and

Sofosbuvir both form metal interaction through the Mg^{+2} with D652 (two interactions) and E702, respectively. This is another reason for the increased stabilization of the formed complexes for IDX-184 and Sofosbuvir. Additionally, Sofosbuvir formed two hydrophobic interactions with Y510 and D651 of the 2019-nCoV RdRp.

To summarize the abovementioned data, we can say that IDX-184, Sofosbuvir, and Ribavirin can tightly bind to the newly emerged coronavirus RdRp and hence contradict the function of the protein leading to viral eradication. Additionally, IDX-184 show more promising results then comes Sofosbuvir as a potent inhibitor against the newly emerged 2019-nCoV strain of HCoV. Further optimization of these two compounds can result in a more potent compound able to stop the newly emerged infection.

Conclusion

The newly emerged coronavirus in Wuhan city in China has a health concern since the last outbreak of these types of viruses (SARS) in the year 2002-2003 in the same country leaving more than 700 deaths and 8000 cases in hospitals. Besides, another outbreak in the Middle East region has an entirely different infection pattern (MERS) leaving more than 800 deaths and 2500 hospitalizations. The present study aimed to test and suggest possible inhibitors, DAA drugs, currently in the market stop the infection immediately. Sofosbuvir and Ribavirin can be used against the new strain of coronavirus that emerged with promising results.

Competing Interest

All the authors declare that there is no competing interest in this work.

Data Availability

The docking structures are available upon request from the corresponding author

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Figure legends:

Figure 1: (A) Multiple sequence alignment of all the HCoV strains (229E, NL63, HKU1, OC43, MERS, SARS and Wuhan 2019-nCoV) RdRp sequences. Red highlights indicate identical residues while yellow highlighted residues are less conserved. Secondary structures are represented at the top of the MSA for SARS RdRp (PDB ID: 6NUR, chain A), while the surface accessibility is shown at the bottom (blue: highly accessible while white is buried). The black dashed rectangles mark active site aspartates while blue rectangles mark the residues lying in the 5Å region surrounding the active aspartates. The alignment is made using the Clustal omega web server and represented by ESpript 3. (B) The newly emerged Wuhan 2019-nCoV RdRp model built by Swiss Model in the green cartoon (right) and surface (left) representations. Two views of the polymerase at 180^{o} rotation on the horizontal plane are shown (top and bottom). The active site aspartates are represented in red sticks for clarification (see the enlarged panel).

Figure 2: Binding energies calculated by AutoDock Vina for GTP, UTP, IDX-184, Sofosbuvir, and Ribavirin against 2019-nCoV (blue) and SARS HCoV (orange) RdRps.

Figure 3: The interactions established after docking the DAA drugs IDX-184, Sofosbuvir, and Ribavirin against 2019-nCoV RdRp. DAAs are in orange while the protein active site pocket in cyan sticks. H-bonds in blue solid lines while hydrophobic interactions are in dashed lines. Salt bridges are in yellow spheres connected by dashed lines. RdRp residues are labelled by its one-letter code and the docking scores are listed under each complex.

Figure 1A

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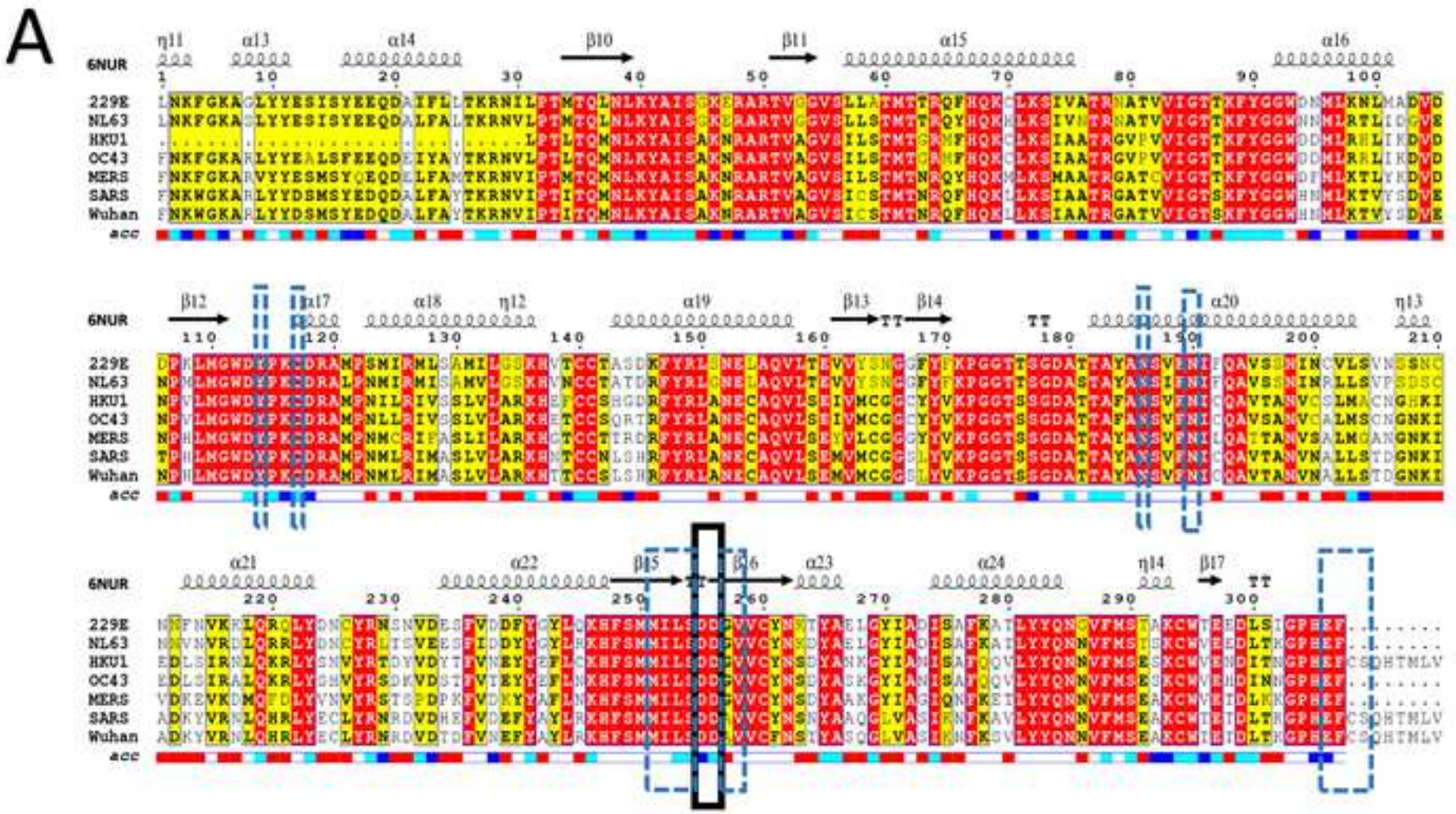

Figure 1B

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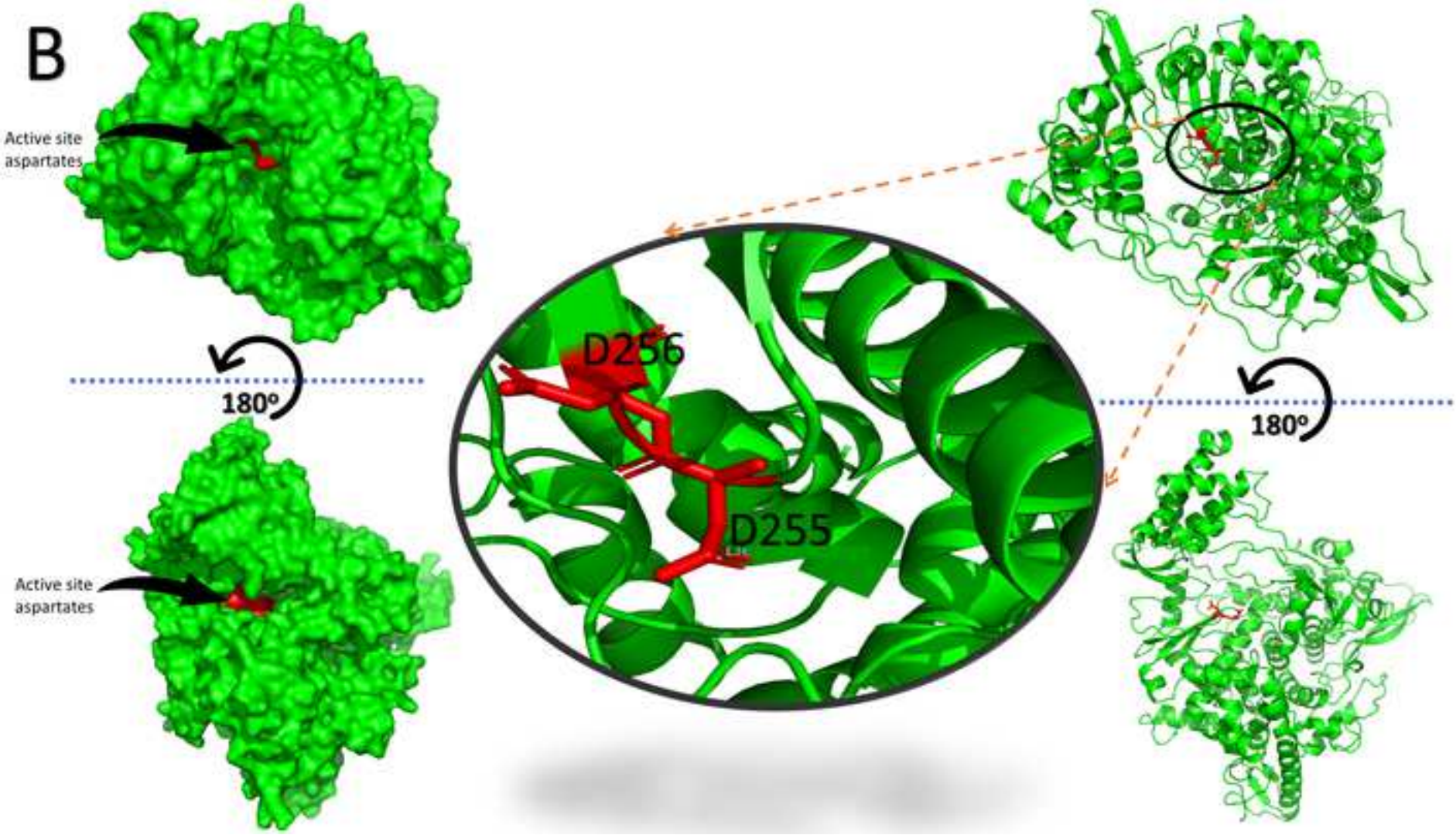


Figure 2

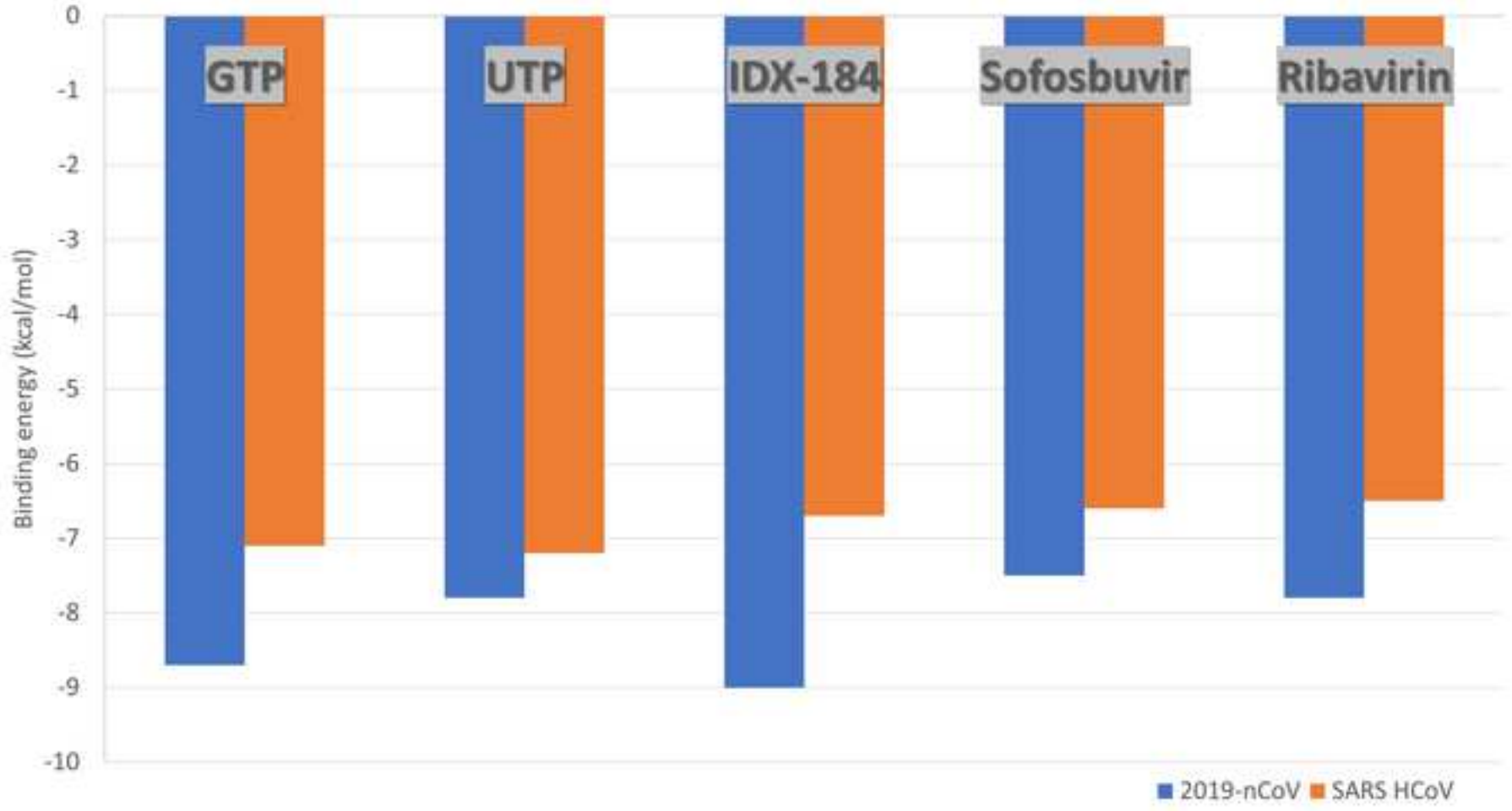
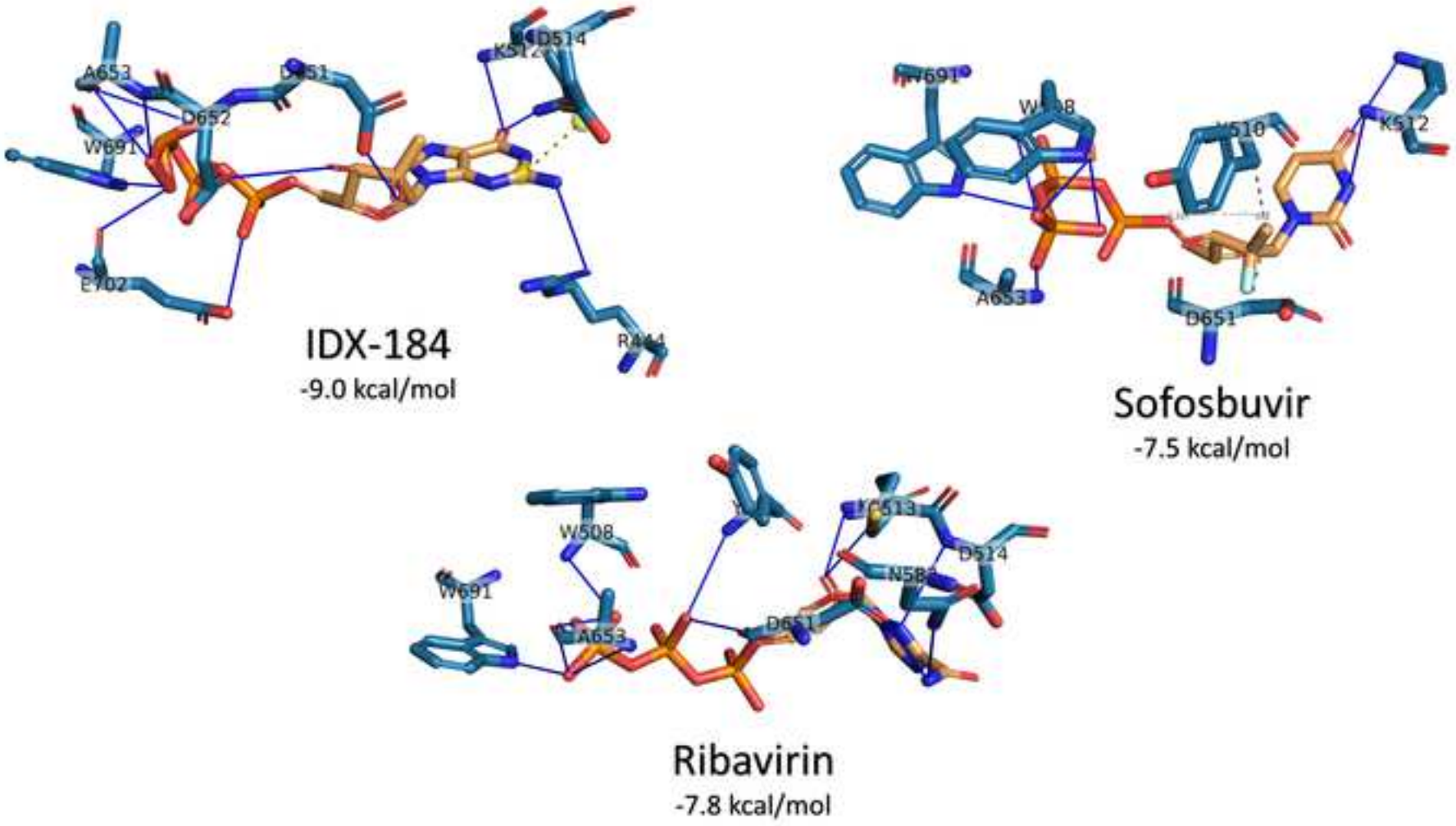


Figure 3



Sofosbuvir can inhibit the newly emerged coronavirus (2019-nCoV) in Wuhan, China

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Research in context

Evidence before the study

Chinese authorities reported a new emerging, novel coronavirus infection to humans in late December 2019. In January, the World Health Organisation (WHO) states a new SARS-like coronavirus outbreak started in Wuhan city in China and posted a surveillance draft and called the new strain of coronavirus 2019-nCoV. Until today (21 January 2020) the number of confirmed infections with the 2019-nCoV is increasing (291 with six deaths) in China, Thailand, and Japan (https://www.independent.co.uk/news/world/asia/coronavirus-news-live-china-latest-virus-wuhan-symptoms-deaths-sars-outbreak-a9293796.html). The availability of the nucleotide gene of the newly emerged strain (posted by NCBI on January 17, 2020) makes it possible to search for homologous RNA dependent RNA polymerase (RdRp) protein. A model for RdRp is built from SARS CoV RdRp and validated to make possible it's testing against inhibitor drugs currently in the market.

Added-value of this study

The availability of FDA approved anti RdRp drug, Sofosbuvir, helps to treat patients and reduce the danger of the mysterious viral infection (2019-nCoV). Sofosbuvir and Ribavirin can tightly bind to 2019-nCoV strain RdRp and can be used to treat the disease. No toxicity measurements are needed since it was already tested before its approval in 2013.

Implications of all the available evidence

The results suggest using Sofosbuvir and Ribavirin against the 2019-nCoV strain. Additionally, new nucleotide inhibitors specific for the new strain of coronavirus can be designed using the RdRp model built from SARS CoV. Based on our results, guanosine nucleotide is a promising seed to get potent anti RdRp compounds.