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Original Article

Virtual Screening and Molecular Docking of FDA Approved Antiviral Drugs for the Identification of Potential Inhibitors of SARS-CoV-2 RNA-MTase Protein

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ABSTRACT

Background: SARS-CoV-2 is a novel coronavirus discovered in December 2019 and is responsible for pandemic disease COVID-19. In the absence of any available vaccines or drugs to combat the virus, it has caused enormous damage.
Methods: An in-silico docking approach was applied to determine potential inhibitors of SARS-CoV-2 RNA-MTase by screening against a ligand library of FDA approved antiviral compounds.
Results: Ten compounds including Daclatasvir, Pibrentasvir, Tenofovir, Velpatasvir, Grazoprevir, Ledipasvir, Elbasvir, Delavirdine, Nilutamide, and Ribavirin triphosphate showed a strong binding affinity with RNA-MTase of which Daclatasvir and Pibrentasvir exhibited the highest affinity. Moreover, Daclatasvir, Grazoprevir, and Tenofovir, which have recently been reported to have a binding affinity with other SARS-CoV-2 proteins, showed good binding interactions with RNA-MTase, suggesting a role to act as dual inhibitors.
Conclusion: The suggested antiviral compounds can tightly bind to RNA-MTase of SARS-Cov-2 and thus have the potential to be used against this deadly virus. Importantly, as FDA already approved, these drugs do not need to undergo toxicity evaluation.
Keywords*:* Antiviral drug, COVID-19, SARS-CoV-2, Novel coronavirus, Nsp10-Nsp16

1. Introduction

Coronaviruses is a large family from *Nidovirales* order that cause conditions ranging from the common cold to severe viral infections [1]. They contain a large conserved genome expressing both structural and non-structural proteins for viral replication [2]. SARS-CoV-2 is a new member of this family involved in the recent spread of the pandemic disease COVID-19 [3]. It is a serious threat worldwide with rapid spreading

rate as evident from consistent increase in its cases [4]. According to World Health Organization (WHO) there are around 1.5 million reported cases of COVID-19 while the death rate has crossed 479 thousand worldwide till June 26, 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019), and is still increasing with the spread of infections in the world. 216 different countries and territories have been affected and there is still no cure available to treat the disease. It started in China but afterward, spread all over the world and USA emerged as its new epicenter in terms of the number of deaths and people affected. Thousands of people are infected and this number continues to grow day by day. Long-term lockdowns and social distancing are some of the major steps to lessen the spread of the disease in the absence of any known effective drugs or vaccine [5].

Due to the unavailability of any vaccine or drugs, WHO recommends quarantine as an effective option for decreasing the spread of the infection? Drugs such as chloroquine and hydroxychloroquine are presumed to be helpful in controlling the COVID-19 but there are still differing views on its efficacy [6]. Furthermore, the virus can develop resistance to drugs with the passage of time and mutations can occur so the availability of multiple drugs would be of paramount importance to combat the disease [7].

People of all age groups are susceptible to coronavirus and it can cause death depending on the severity of infection in patients [8]. People suffering from chronic diseases such as diabetes and blood pressure are severely affected with higher death ratio as compared with healthy individuals. The symptoms of infection vary from person to person [9]. The first category includes the people that are the carrier of the virus with no apparent symptoms. The next category comprises people with infection in the upper respiratory tract and develops pyrexia, cough, and fatigue. The third category includes people with flu-like symptoms who could develop pneumonia and have severe breathing problems [10]. The effect of the current COVID-19 outbreak and the possibility of future potential epidemics, strongly support the rapid creation of new drugs and rapid intervention protocols. Different research groups have exploited the repertoire of already existing drugs to discover therapeutic agents against this deadly virus. For this purpose, besides experimental investigation of the potential drugs [11, 12], an important and comparatively fast strategy is to virtually screen out the therapeutic compounds against the possible drug target proteins of this virus [13-15] for designing potential drugs.

SARS-CoV-2 contains different proteins including spike proteins, envelope proteins, membrane proteins and nucleocapsid proteins [16]. Spike proteins help to enter in the human cell for replication by attachment to receptors present on the host cell membrane [17]. Membrane proteins are involved in shape formation of virion while replication [18]. Similarly, other proteins are performing significant functions for the replication and survival of coronavirus in the host. Targeting specific proteins involved in important functions is a key parameter utilized for the demise of an organism [19]. For this study, we selected a significant protein that helps SARS-CoV-2 to obscure from the defense system of the host and thus replicates easily. This protein is termed as RNA-methyltransferase or MTase protein that transfers the methyl group for cap structure generation. Inhibition of the proposed protein could lead to the detection of SARS-CoV-2 as a foreign

pathogen and the immune system will activate to combat the viral infection.

The current work reports drug repurposing approach targeting a novel important SARS-CoV-2 protein namely RNA-MTase as a drug target to investigate FDA approved antiviral drugs for aiding in drug development against the current pandemic disease COVID-19.

2. Materials And Methods

2.1 Retrieval of Protein structure

RNA-MTase was selected as a drug target protein for analysis. The crystal structure of RNA-methyltransferase protein was obtained from PDB (6W4H). The protein consists of two chains with ligands including two zinc fingers, acetate ion and sulfate ion in its structure. Moreover, Beta-D-fructopyranose and S-Adenosylmethionine are also attached to the target protein. The protein target was analyzed by using Rasmol [20]. Rasmol is a graphic program for visualization of three-dimensional protein structures that helps to display the macromolecule by different visualizing schemes and representations.

2.2 Active site determination of MTase protein

Active site determination is significant to identify the catalytic domain of the protein. Computed Atlas for Surface Topography of Proteins (CASTp) determines the pockets of the protein that are located either on the surface or reside inside the domain by using models of Richard surface and Conolly's surface [21]. It analytically calculates and measures the regions and predicts the best functional regions of the protein. It was employed to analyze the active site and determine the amino acid residues of pocket in the catalytic domain.

2.3 Datasets preparation for virtual screening

Clustal W2 is an easily accessible multiple sequence alignment tool that assists to compare divergent protein/DNA sequences and determine a similarity between them [22]. RNA-MTase protein was compared with other coronaviruses and high similarity was found with SARS. To compare the binding interaction of the ligands, two previously reported inhibitors namely Sinfungin and Aurintricraboxylic acid (ATA) [23] were selected as standards based on the similarity between our target protein and MTase protein of SARS. FDA approved 82 antiviral drugs were retrieved from the drug bank for preparing the ligands library.

2.4 Protein and Ligands optimization

The energies for both protein and selected ligands were optimized using Molecular Operating Environment (MOE) software. Energy minimization was performed to obtain the stable conformation of RNA-MTase and ligands. For docking analysis, the target protein was edited by removing water molecules and other attached atoms. Protonation of the target protein as well as the ligands were also performed.

2.5 Docking analysis of MTase protein

The molecular docking approach facilitates comprehending the biochemical interactions between proteins and ligands [24]. Docking predicts the ligand conformation as well as the binding affinity of a ligand with the target protein [25]. Herein, docking analysis for SARS-CoV2 MTase protein with selective ligands library was performed via the Molecular Operating Environment (MOE) [26]. MOE is a highly accurate prediction tool for the analysis of biological activities of molecules and mostly used in virtual scanning of

molecules for drug designing. For analysis, the induced-fit method was selected with two poses limit and all ligands were docked simultaneously with MTase protein. Binding energies and interactions were analyzed for the selection of potential drugs.

3. Results and Discussion

This study proposed some inhibitors by the computational molecular docking approach that could serve as leading compounds against SARS-CoV-2 pathogen. RNA-MTase (Nsp10-Nsp16) is a novel protein of this pathogen that could act as a drug target and its 3D structure was recently deposited to PDB (6W4H). It is a dimer of two non-structural proteins (Nsp) termed Nsp10 and Nsp16, which is involved in the viral replication process. It performs methylation activity for cap generation at ribose 2'O position of viral RNA. SARS-CoV-2 hides from the immune system by expressing protein RNA-methyltransferase (MTase) that is involved in cap generation and makes viral RNA like eukaryotes [27]. Inhibition of RNA-methyltransferase (Nsp10/16) may lead to inhibition of methylation at cap structure that makes viral genome susceptible to degradation by host-encoded ribonucleases or might become non-functional for protein production [28].

3.1. Retrieval of RNA-MTase

The functional feature of RNA-MTase protein makes it an active drug target. The crystal structure of the protein was retrieved from PDB (6W4H) and analyzed through Rasmol graphic viewer before further processing.

3.2 Active site determination

RNA-MTase has methylation activity; therefore, CASTp was used to determine the catalytic pocket (Figure 1). Investigation through CASTp server revealed ASN6841, LYS6844, TYR6845, HIS6867, PHE6868, GLY6869, ALA6870, GLY6871, SER6872, ASP6873, PRO6878, GLY6879, SER6896, ASP6897, LEU6898, ASN6899, ASP6900, PHE6901, GLY6911, ASP6912, CYS6913, ASP6928,

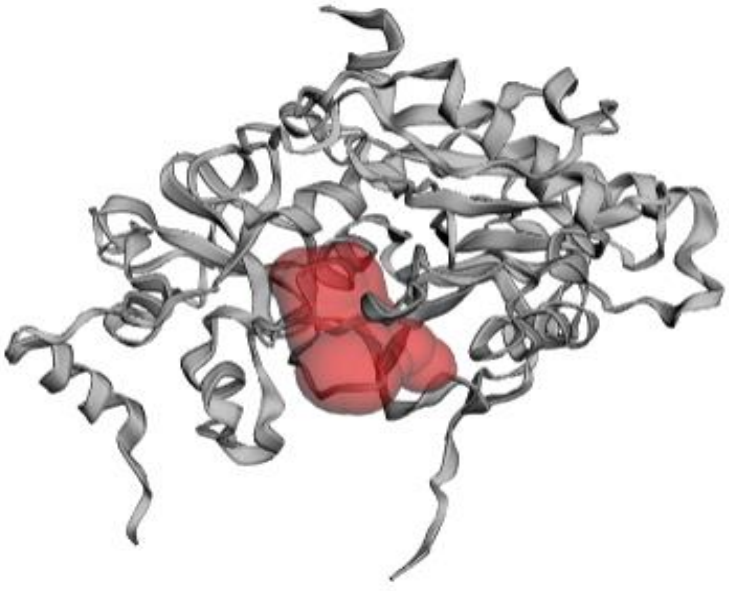


Figure 1. RNA-MTase active site determined by CASTp server. The red area specifies the predicted pocket for ligand attachment in the catalytic domain.

MET6929, TYR6930, ASP6931, PRO6932, LYS6933, PHE6947 and LYS6968 amino acid residues as a fragment of the binding pocket of the protein involved in catalytic activity.

3.3 Dataset preparation for in-silico analysis

RNA-MTase protein of SARS-CoV-2 was compared with the proteins of other coronaviruses through Clustal W2 server. Multiple sequence alignment showed the highest similarity index by approximately 93% with SARS RNA-MTase. Many in-vitro attempts were made to design inhibitors for SARS RNA-MTase including Sinfungin and ATA. The antiviral effects of both compounds were studied *in-vitro* in *E.coli* cells infected by SARS coronavirus. Sinfungin and ATA showed minimum IC_{50} values of 736 nM and 2.1 μM for RNA-MTase in the performed assay [29]. Based on the high similarity between the two proteins, the two tested inhibitors of the SARS MTase namely Sinfungin and ATA were used as standard inhibitors in this study.

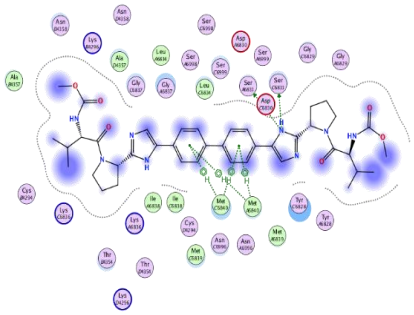
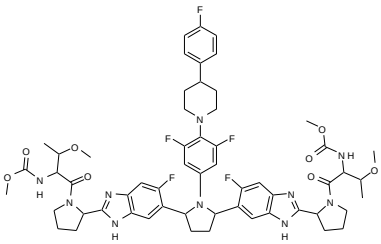
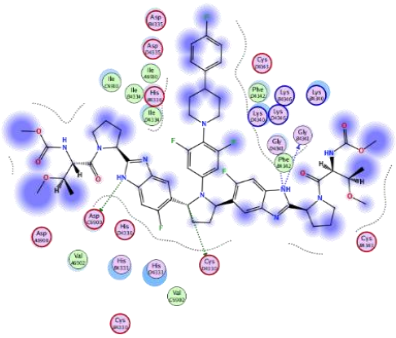
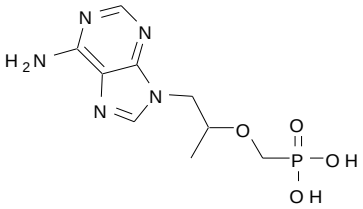
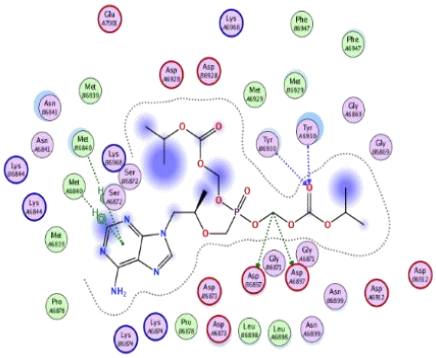
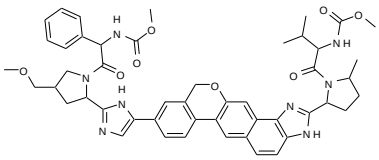
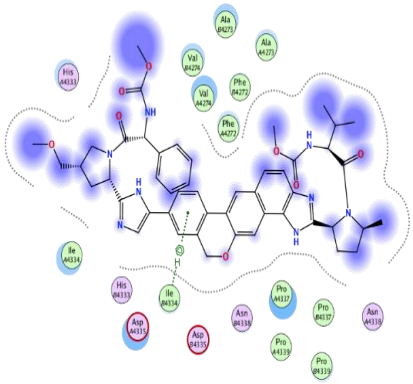
A comprehensive ligand library of 84 antiviral compounds was constructed by retrieving the 82 FDA approved antiviral drugs from the Drug bank and two experimentally proved inhibitors of RNA-MTase that were used with the purpose of comparison.

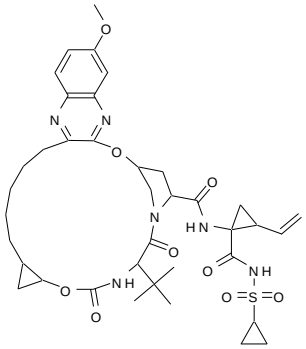
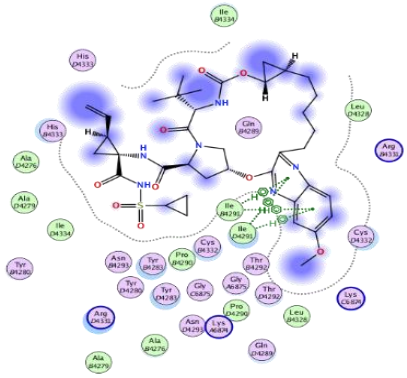
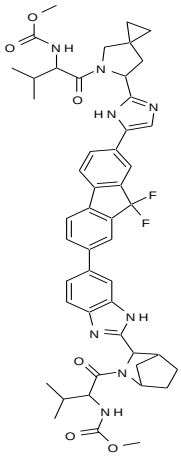
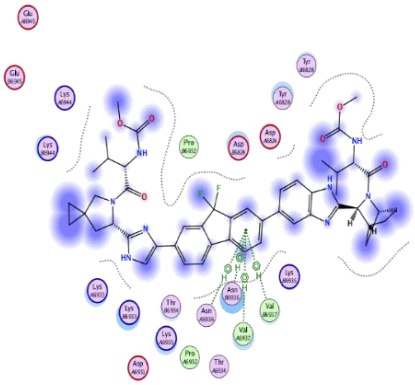
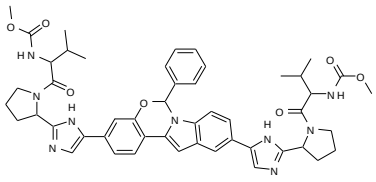
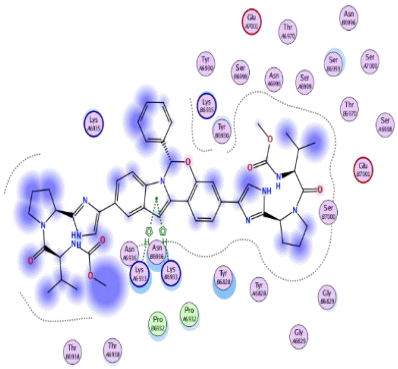
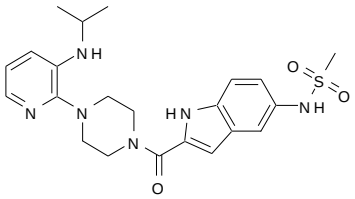
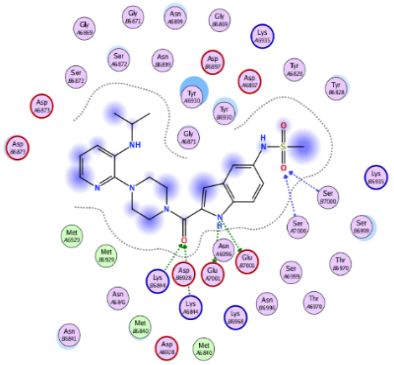
3.4 Optimization and Docking analysis of RNA-MTase

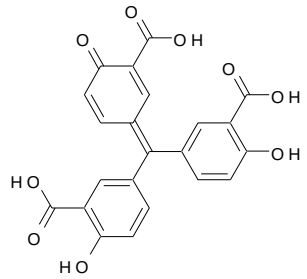
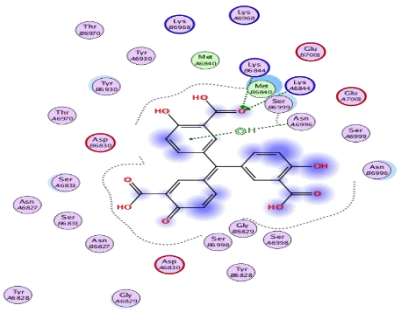
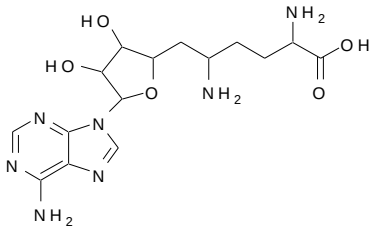
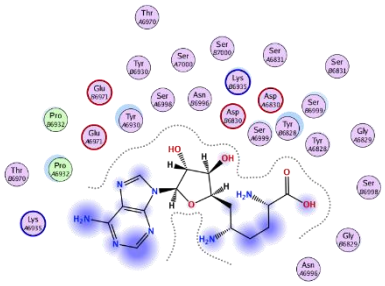
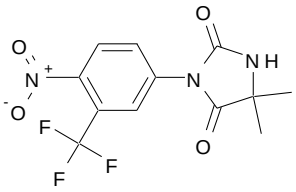
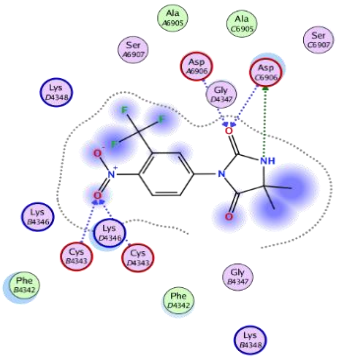
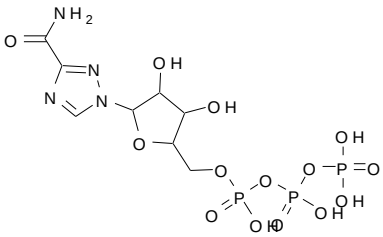
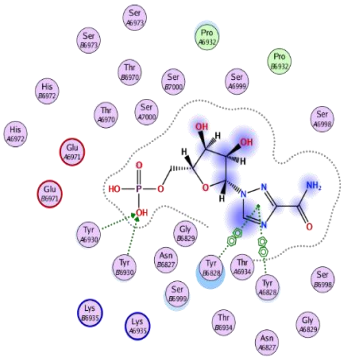
Protein and Ligands were optimized and docking approach was performed using MOE server. Docking results with FDA approved drugs indicated ten compounds namely Daclatasvir, Pibrentasvir, Tenofovir, Velpatasvir, Grazoprevir, Ledipasvir, Elbasvir, Delavirdine, Nilutamide and Ribavirin triphosphate with the highest binding energy as top putative drugs that showed the best potential as leading compounds for inhibition of RNA-MTase (Table 1). The binding energy of the ATA was comparatively less from that of the eight potential drugs in analysis proving them as top-scoring compounds with more potential to inhibit this important viral enzyme. Out of ten scoring drugs, six drugs were the part of combination therapies for the treatment of Hepatitis C infection [30].

Tenofovir is a phosphate donor for nitrogenous bases and nucleotide analog of adenosine monophosphate. It is taken in oral form for treatment against HBV, Herpes virus and HIV [31]. It is important to note that tenofovir is reported to have the potential of inhibiting another important enzyme of the SARS-CoV-2 namely RNA dependent RNA polymerase [32], suggesting the potential of this drug as a dual inhibitor of two different enzymes of the virus, hence justifying further investigation as a novel drug against SARS-CoV-2. Another drug, namely Grazoprevir, has also presented good binding interaction with MTase as well as recently reported with other SARS-CoV-2 enzymes as well [33], indicating its potential of targeting multiple enzymes of the virus. Elvitegravir is used for the treatment of HIV-1 infections as approved by FDA in 2012 [34].

Table 1. Top scoring FDA approved antiviral drugs against RNA-MTase protein.

Sr. No.	Compound Structure & Name	Pubchem ID	Molecular interaction	Docking Score
1	 Daclatasvir	25154714		-7.9719
2	 Pibrentasvir	58031952		-7.8545
3	 Tenofovir	464205		-7.5485
4	 Velpatasvir	67683363		-7.5237

5	 Grazoprevir	44603531		-7.4162
6	 Ledipasvir	67505836		-7.2898
7	 Elbasvir	71661251		-7.2707
8	 Delavirdine	5625		-6.7539

9	 Aurin Tricarboxylic acid (ATA)	363942		-5.6043
10	 Sinefungin	65482		-5.5418
11	 Nilutamide	4493		-5.2331
12	 Ribavirin triphosphate	122108		-5.2244

Similarly, Delavirdine is a non-nucleoside inhibitor that is effective against HIV-1 virus [32]. Based on our analysis, of the top-scoring compounds, two of them with the highest binding energies, i.e. daclatasvir and pibrentasvir, are proposed as potential inhibitors for RNA-MTase to be further investigated for use against this virus.

Daclatasvir, an antiviral compound, showed strong binding affinity by forming a strong interaction with Ser6831 residue by donating two hydrogens simultaneously to Chain A of the receptor (Figure 2). Its benzene ring

displayed the arene hydrogen bond interaction with Met6840 residues. Daclatasvir presented a total of four pi bonds with different atoms of receptor and acidic side chain donor interactions with RNA. Along with these interactions, this complex also indicated some hydrophobic interactions with multiple amino acid residues including AlaB4357, AsnB4358, LysB4296, AsnD4358, AlaD4357, GlyC6837, LeuA6834, GlyA6837, SerA6998 and Ser6C998 among the others (Figure 2). These electrostatic and hydrophobic interactions make this compound being highly active and suitable for experimental verification.

Daclatasvir is an antiviral agent used for the treatment of Hepatitis C recognized by the market name of daklinza. It is the first safe drug against Hepatitis C virus that was approved by FDA in July 2015 [33]. Importantly, this antiviral drug has been recently reported to have binding interactions with other COVID-19 enzymes, suggesting it as more potent inhibitors of the virus [15]. Following this compound, the docked complex of second potential drug, i.e. Pibrentasvir with viral protein, showed the second-highest docking score because of its donating capacity to Cys4330 and Gly4341 residue on B chain of the receptor (Fig. 3). This complex demonstrated the side-chain hydrogen donating ability to acidic amino acid residue Asp6900 of A chain receptor. Besides these amino acids, several others such as AspB4335, AspD4335, IleA6910, HisB4336, IleD4334, IleB4334, IleC6910, AspA6900, ValA6902, HisB1333, HisD4336, HisD4333, ValC6902, CysB4330, CysD4343, PheD4342, LysB4346, LysB1340, LysD4346, LysD4346, GlyB4341, GlyD4340, GlyD4341, PheB1342, and CysB1343 are involved in hydrophobic interactions.

Pibrentasvir is also an antiviral compound against HCV and works by inhibition of non-structural protein functionality. It is also an FDA approved drug for Hepatitis C treatment in patients without liver or kidney diseases [34]. The two above mentioned FDA approved antiviral compounds need to be experimentally validated against SARS-CoV-2 due to their potential of strong binding affinity with RNA-MTase enzyme. Two potent reported synthetic compounds that were experimentally shown to inhibit the SARS MTase protein were used as standard inhibitors for comparison [23]. Out of the two standards, ATA exhibited higher binding energy and stronger hydrophilic interaction as a polar side chain acceptor with Lys6844 residue and arene-H interaction with Asn6996 residue. ATA formed a bond with receptor protein through different hydrophobic residues (Figure 4). It is important to note that out of ten leading compounds eight showed the highest binding interactions than the standard compounds used in this analysis (Table 1).

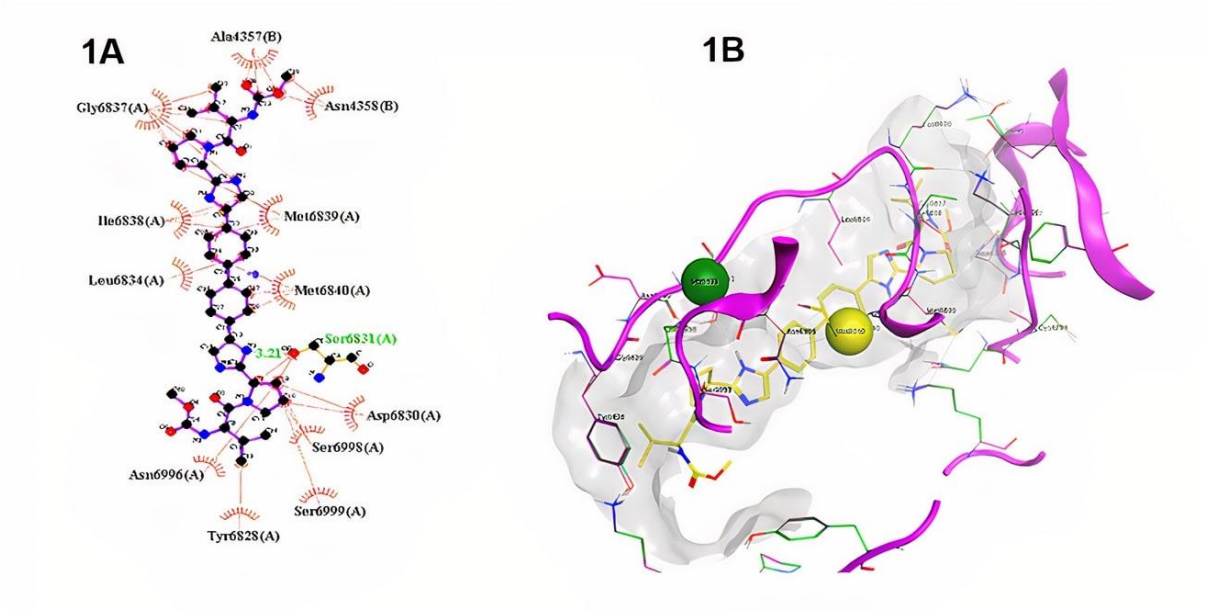


Figure 2. The daclatasvir binding interactions to the active site residues of RNA-MTase. (1A) Show key residues interacting with the ligand molecule. (1B) Grey colored molecular area shows the binding cleft of RNA-MTase while interacting amino acid residues are shown in the yellow-colored ball.

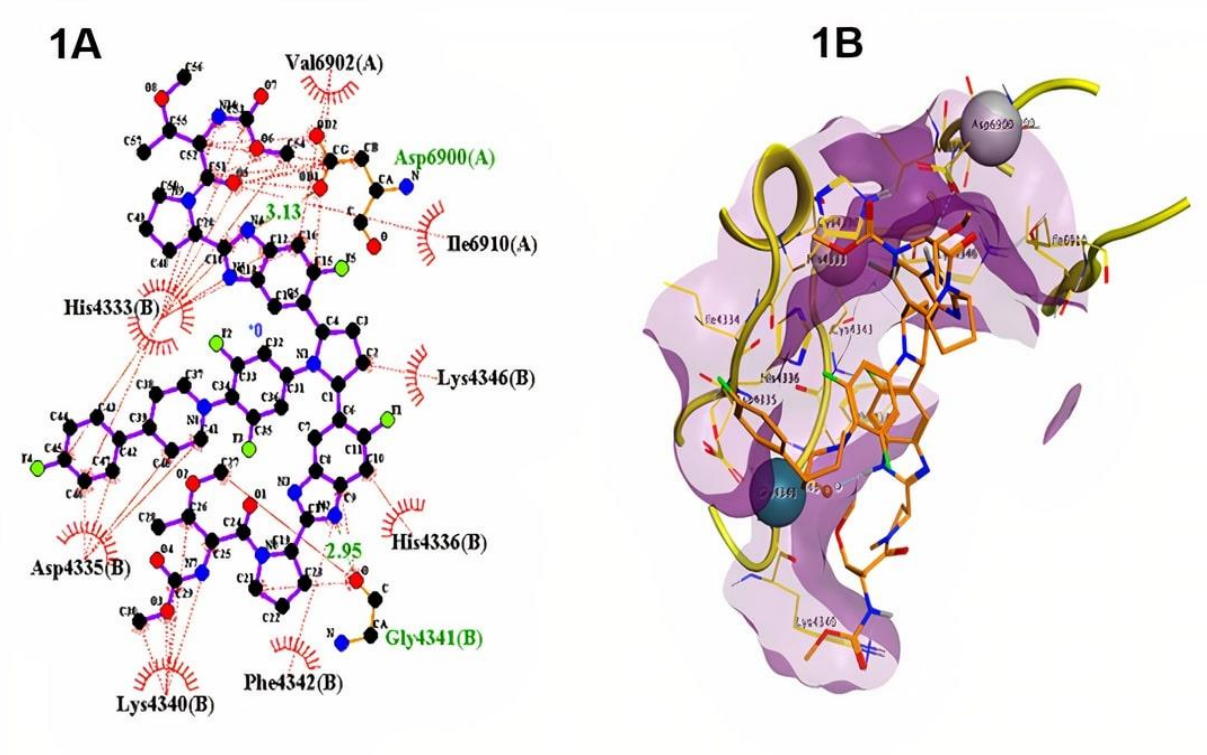


Figure 3. The Pibrentasvir binding interaction to the active site residues of RNA-MTase. (1A) signifies key residues interactions with the ligand molecule. (1B) denotes the purple molecular surface has key residues interacting with ligand shown in orange color.

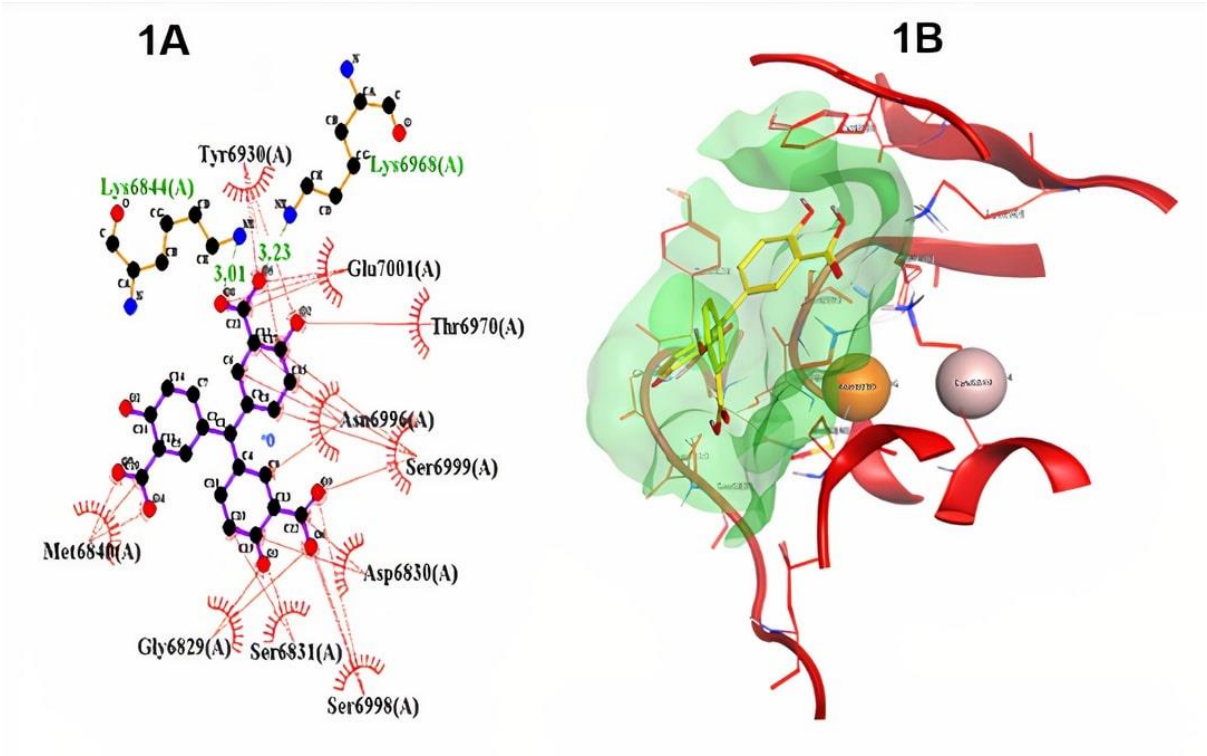


Figure 4. Binding interactions of Aurintricraboxylic acid with active site residues of RNA-MTase protein. (1A) represents key residues interactions of the ligand with the target protein and (1B) signifies green molecular surface contains key residues interacting with ligand shown in yellow color

4. Conclusions

The systematic screening of FDA approved antiviral compounds against RNA-MTase illustrated that Daclatasvir, Pibrentasvir, Tenofovir, Velpatasvir, Grazoprevir, Ledipasvir, Elbasvir, Delavirdine, Nilutamide, and Ribavirin triphosphate could strongly bound with viral protein and block the replicating pathway of viral RNA-MTase. Moreover, Daclatasvir, Grazoprevir, and tenofovir which are recently reported to have the potential of inhibiting other SARS-CoV-2 enzymes had the potential of targeting multiple target proteins of the virus and hence could act more efficiently. Herein, these candidate compounds are predicted as leading inhibitors for MTase protein of SARS-CoV-2 and deserve further experimental evaluation to be used as drugs against COVID-19.

Abbreviation

Not applicable

Conflict of interest

All authors declare no conflict of interest exists.

Consent for publications

All author(s) read and approved the final manuscript for publication.

Availability of data and material

All data generated during this study are included in this published article.

Authors' contributions

S.J, S.W and S.B have executed the research activities. M.S.J, A.A and H.N edited the manuscript. M.S and U.N designed the study and approved the final version of the manuscript.

Ethics approval and consent to participate

No human or animals were used in the present research.

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