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Comparative Study of Drug Likeness and Pharmacokinetic Properties of Synthetic Antiviral Drugs to that of Remdesivir: In-silico Approach

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

COVID-19's recent appearance in Wuhan, China, has affected more than three million twenty-five million individuals worldwide. It is considered a pandemic disease by WHO. Till now, there is no approved therapeutic for treating COVID-19 infection. The involvement of RNA-dependent RNA polymerase in coronavirus replication is crucial, and it could be a potential therapeutic target. To identify potent inhibitors against coronavirus, we have applied a molecular docking tool targeting RdRp by antiviral synthetic ligands and phytochemical ligands. Auto Dock 4.2.6 was used to do molecular docking in order to predict the most effective drug. In the present study, molecular docking studies of fifty ligands against the protein RNA dependent RNA polymerase. A comparative study was done using standard antiviral ligands Remdesivir. Out of fifty ligands, the top ten compounds were selected, which shows maximum binding affinity.Furthermore, ADME analysis and Lipinski's five rules were investigated to check the drug-likeness and pharmacokinetic properties of the top ten ligands. We observed from the following results that except few, all the ligands showed the best binding energy compared to standard ligands against coronavirus. Depending on the higher docking score, ADMET and drug-likeness prediction top five ligands were selected. This study will provide a lead molecule against RNA-dependent RNA polymerase for further in-vivo and in-vitro of coronavirus.

Keywords: COVID-19RNA dependent RNA polymerase; ADME; Lipinski's 5 rule; molecular docking.

ABBREVIATIONS

ADME : Absorption, Distribution, Metabolism, Excretion and Toxicity
MER-CoV: Middle East Respiratory Syndrome Coronavirus

1. INTRODUCTION

At the turn of the twenty-first century At the beginning of the twenty-first century, millions of individuals were infected with the newly discovered coronavirus infection 2019 (COVID-19) [1], it was first detected in China's Hubei province Wuhan, the metropolitan region. It has been widely spread from China to many other countries, and it has been drawing enormous attention all around the globe [2]. According to the WHO, this viral disease is considered very pandemic [3].

In the closing 20 years, numerous viral epidemics, including the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003 in Guangdong province, China, and H1N1 influenza in 2009, have been recorded. In 2002 SARS appeared in Southern China and spread to twenty-eight other countries. By July 2003, almost 8,000 individuals had been inflamed, with 774 of them dying. Only four cases were observed in the small outburst in 2004 [4]. Ten years after SARS, another highly infectious pathogenic coronaviruses, MER-CoV, emerged in Middle Eastern countries [5]. It was started in 2012 in Saudi Arabia. More than 1621 cases were infected; 584 people died in 2012 due to middle-east respiratory syndrome coronavirus. Compared to SARS, it was less contagious [6,7]. SARS-CoVs and MERS-CoVs are Zoonotic viruses with bat/cat and dromedary camel as hosts, respectively [7,8]. After SARS-CoV and MERS-CoV,the COVID-19 is said to be the third zoonotic coronavirus [9]. Commonly reported symptoms of a person infected with COVID-19 are runny nose, cough, fever, headache, and shortness of breath. After infection with COVID-19, depending on a person's age and weak immunity, the symptoms appear within 2 to 14 days [10]. Patients with mild symptoms will cure within a week, while in severe conditions, the respiratory system will fail due to the alveolar damage triggered by the virus. This may lead to the demise of patients [11].

Coronaviruses are a broad family of viruses that may infect people and a wide variety of animals. Coronavirus belongs to the subfamily Coronaviridae within the own family of Coronaviridae the order Nidovirales. CoVs are divided into four genera: Alphacoronavirus, Betacoronavirus, Gamma Coronavirus, and Deltacoronavirus based on their genomic and phylogenetic relationship [12]. Generally, mammals are infected by the genera Alphacoronavirus and Betacoronavirus. The Gammaoronavirus and Deltacoronavirus can infect birds, but some of them can also infect mammals [5]. On January 12, 2020, WHO named the novel coronavirus as 2019 novel coronavirus or '2019-nCoV', then on February 11 2020 the ICTV(International Virus Classification

Commission) labelled 2019-nCoV as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) according to the guidelines of nomenclature of virus because 2019-nCoV is homologous with SARS-CoV. At the same time, 2019-nCoV-related diseases were designated as COVID-19 by WHO [1].

Coronavirus is a single-stranded RNA virus (+ssRNA), which is about 120nm in diameter. It poses the giant genomes ~26kb to ~32kb among all the known RNA viruses, and it contains a 3' poly-A tail and a 5' cap structure that allows it to act as mRNA to translate polyprotein [13]. The first CoVs were identified in the 1960s by a group of virologists. Depending upon their morphological features, they represent spherical virion with a center shell. The spike, which is protein present on the virus's surface, resembles a crown; the virus has termed the corona; corona in ancient Latin language means crown based on their shape [1]. The positive single-stranded RNA genome of CoVs encodes the 2 significant genes, i.e., OPF1a and ORF1b, which encodes 16nsp (non-structural protein). ORF1a encodes form nsp1-nsp11 and ORF1b encode for nsp12-nsp16 [14,15].

The CoVs structural genes encode the four structural proteins, Spike (S) protein, Membrane protein (M), Nucleocapsid protein (N), and the Envelope protein (P). Some of the beta coronaviruses also have an additional layer of the short spike, consisting of the hemagglutinin esterase protein (HE). These are all required to complete the structure of viral particles [16]. Several functional CoVs proteins are involved in translation, modification of RNA, synthesis, transcription, virus replication, and infections. Among these, PLpro (papain-like protease), 3CLpro (3-chymotrypsin-like protease), RdRp (RNA dependent RNA polymerase), and helicase are the most critical targets for the development of inhibitors [17]. RNA-dependent RNA polymerase plays a vital role in SARS-CoV-2, which acts as a replica that catalyzes the synthesis of a complementary RNA strand using an RNA template for replication and transcription. Thus it can be used as a potent drug target [18,19].

In this study, we archiveda molecular docking to test the several synthetic and photochemical antiviral drugs against the RdRp (RNA dependent RNA polymerase) protein of coronaviruses. In the present study we used the human immune virus (HIV) compounds, anti-malarial compounds, and also the earlier reported anti-SARS-CoV and anti-MERS-CoV synthetic compounds and some of the antiviral phytochemicals chosen randomly. The obtain results provides a new repurposed drugs against SARS- CoV-2 using *in-silico* approach.

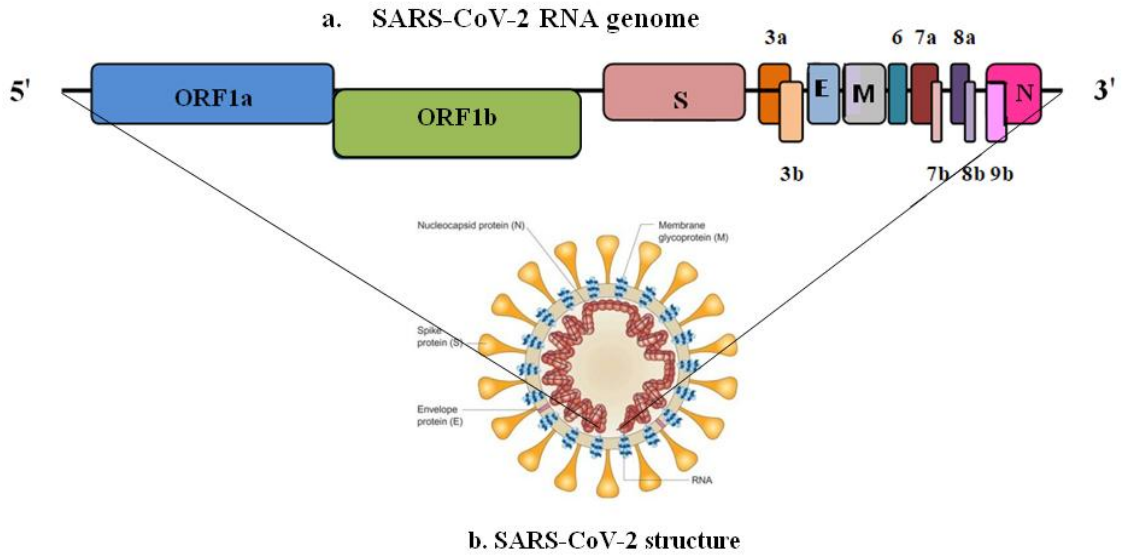


Fig.1. SARS-CoV-2 RNA genome and structure. a) Schematic representation of the RNA genome. The 2 large genes ORF1a (blue) and ORF1b (green)are encoded in the genome, it codes for 16 non-structural proteins (NSP1-NSP16) and the structural gene encodes the structural proteins [Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N)] and other accessory proteins, which are unique to SARS-CoV-2. b) Schematic representation of SARS-CoV-2 structure [20]

2. MATERIALS AND METHODS

2.1 Protein Preparation

Coronavirus (COVID-19) related articles were referred to identify the target proteins, after the identification of target protein the 3D structure of RdRp from COVID-19 (PDB code: 6NUR) with the resolution 3.10 Å. The target protein 6NUR was downloaded from the PDB in the PDB file format. Then the saved PDB format of protein was opened in PyMOL. In PyMOL all the ligands, ions, and nsp12 protein was cleaned by removing the water molecules. Then the protein structure was saved in the PDB format[21]. Then the protein 6NUR was opened in AutoDock 4.2.6 to see the docking results.

2.2 Ligand Preparation

The 3D structure of each compound is downloaded in SDF format from the PubChem and then converted into PDB format using Open Babel free software. The ligand should be in the PDB format. Finally, the PDB formats of ligands are opened in AutoDock4.2.6. The ligands selected for molecular docking of RdRp are anti-HIV, anti-malarial, and also some of photochemical against anti-viral. The high similarities between the main protein of SARS-CoVs or MERS-CoVs and the recent COVID-19 we also selected the ligand of anti-SARS-CoVs and anti-MERS-CoVs[21,3].

2.3 Grid Box Generation

Blind-docking with a search method in AutoDock 4.2.6 was used to calculate the binding site. Primarily, binding site was determined from reading from various Articles related to COVID-19 and docked in the previously ligand binding site of protein was used to dock the selected ligand molecules. Using AutoDock software 4.2.6, a grid box was created around the ligand binding site by changing the grid settings for the X, Y, and Z coordinates [22].The grid center of the RdRp (RNA dependent RNA polymerase) enzyme has the highest affinity binding site at co-ordinates of X=150.009; Y=147.554; and Z=157.012 with a 3D grid box of 30 x 30 x 30[17]. The best binding energy conformation of the ligand molecule which had a lower calculated binding energy (negative energy) as compared to the reference molecule was selected for further analysis and considers having a higher binding affinity with the target NSP12 molecule[3].

2.4 Molecular Docking

AutoDock 4.2.6 software was used to check the inhibiting ligand against coronavirus virus RdRp as the docking target. The protein structures were opened in the AutoDock and then were prepared for docking by removing the water molecules from the protein, then add the polar hydrogen and the compute Gasteiger charges. Then open the ligand and save both the ligand and the protein in the pdbqt format. Then set the grid box, save the file in. GPF format andDPFformat. Then run the docking in autogridandautodock pathname. The complex of protein-ligand was formed. The pose with lowest calculated energy of binding affinity was selected and then saved as PDB format. Then obtained docked poses were analyses using the PyMOL software[23].

2.5 ADME Properties

ADMET full form Absorption, Distribution, metabolism, Excretion and Toxicity. The toxicity of the bio reactive compounds is determined with the help ofPreADMET. In drug design, and drug discovery process ADMET play an important role because 60% failure of all the drugs in the pre-clinical phaseis due to these properties. Nowadays ADEM is applied at the early stage of the drug development, and discovery process.

Four main partsofPreADMET are as follows: Molecular descriptor calculation, drug-likeness prediction, ADME prediction, and toxicity prediction [2]. The drug likeness prediction of certain compounds that have a certain pharmacological activity was calculated using Lipinski's rule of 5. The rules states that 1) Not more than 5 H-bond donors(OH and NH) 2) Not more than 15 rotatable bonds 3) Not more than 10 H-bond acceptors 4) Amolecular weight of compound should be less than 500g/mol 5) A partition coefficient(log P) should not be less than 5 [24,25].

2.6 Docking Visualization and Analysis

Visualization and analysis of the docking site was performed by using PyMOLandAutoDock was used for result validation. The interaction between the protein and ligand was checked usingPyMOL along with bond length and the amino acid residue to which the ligand binds to the protein[2][3]. The visual analysis of two-dimensional molecular interactions between the protein-ligand complex structures was performed using BIOVIA Discovery studio visualizer

software. It also used to depict the hydrogen bonds, hydrophobic bonds of each molecular docking poses in the form of graphical representation.

3. RESULT AND DISCUSSION

3.1 Selection of Protein and Ligand for Docking Analysis

Coronaviruses are grouped under the viruses which can infect humans. Lakhs of people were killed all around the world. COVID-19 pandemic is the most damaging pandemic in recent human history. Our research points to the RNA dependent RNA polymerase protein in coronavirus (RdRp/nsp12) as a possible therapeutic target for the development of efficient antiviral medicines in the context of coronavirus infection (PDB ID: 6NUR). 6NUR is one of the main proteins in the coronavirus. RdRp plays a vital role inproliferation in the life cycle of coronavirus by RNA replication. RdRp consist of 3 unique chains, i.e., nsp12, nsp8 and nsp7, it also consists of 2 Zinc atoms **(Fig. 2).** The nsp12 bound to the nsp7 and nsp8, the resolution is 3.10 Å, total structural weight is 162.52kDa and it as 1087 amino acid residues. Therefore, RNA dependent RNA polymerase is ideal as therapeutic targets to identify the inhibitors for coronavirus, by this we can stop the spreading of virus in the human body. Therefore, a basic preliminary screening of ligands was carried out by using Autodock4.2.6, selected50 synthetic ligands, were studied against the target protein RNA dependent RNA polymerase of COVID-19 **(Fig. 3)**

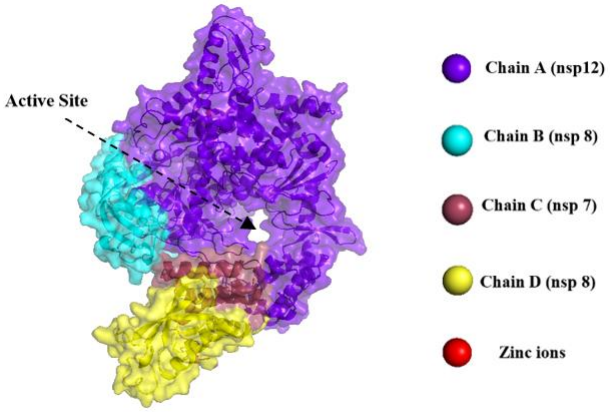


Fig. 2. Structure of coronavirus RdRp protein/nsp12 complex with co- factors nsp7 and nsp8. Chain A highlighted in purple colour, Chain B is highlighted in cyan colour, Chain C is shows as raspberry colour, and chain D shows as yellow colour

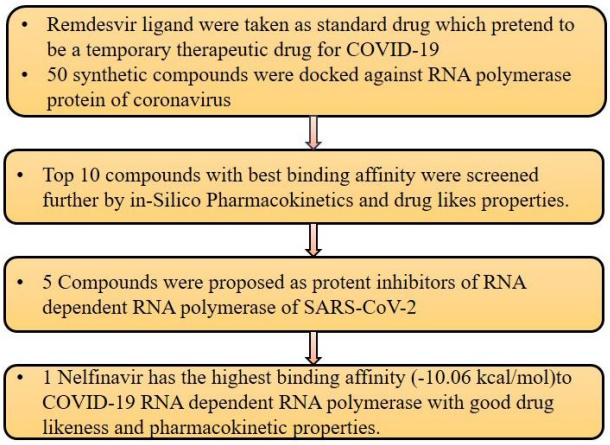


Fig. 3. Schematic representation showing the steps of screen Synthetic ligands for the SARS-CoV-2

3.2 Molecular Docking Analysis

To search potential inhibitor for SARS-CoV-2, total fifty synthetic ligands were selected for docking analysis using the Autodock 4.2.6 computational screening against the important protein RdRp. Considering the biological activity like anti-MERS, Anti-SARS, Anti-HIV, anti-malarial and antiviral agents we have selected the ligands. The majority of the inhibitors exhibited greater than -6.48 kcal/mol in the docking findings of fifty ligands against the RdRp target, and the results were comparable to the conventional medication Remdesivir, which pretended to be a transitory therapeutic treatment. As the core part of all the ligands were similar, ten ligands which showed the maximum docking score against the protein RdRp were considered for further *in-silico* ADMET and drug likeness study**.** 2D chemical structureof the selected lead compounds are represented in **Fig. 4**.A graphical representation of top 10 ligands shows the average binding affinity of ligands which inhibit the protein RdRp are represented in **Fig. 5**.

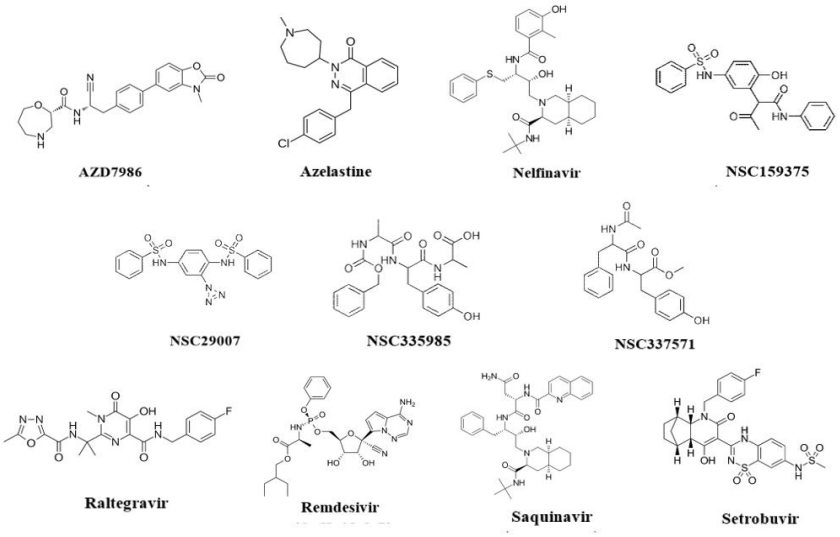


Fig.4. The alphabetical list of 2D chemical structure for the top ten ligands which showed the high docking score against the RNA dependent RNA polymerase protein of coronavirus, including Remdesivir ligand claimed to be effective for COVID-19

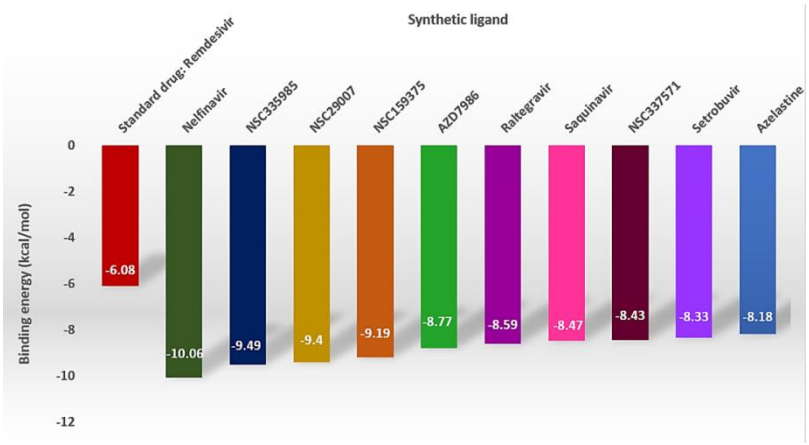


Fig.5. A graph representing the top ten ligands which showed the maximum binding energy(kcal/mol) calculated by using Autodock4.2 software. The Nelfinavir (dark green column) ligand shows the highest docking affinity (-10.06kcal/mol) to RdRp. The standard drug Remdesivir (-6.08kcal/mol) are depicted in red column

3.3 ADME Properties and Analysis

The selected compounds were analysed after molecular docking with the protein RNA dependent RNA polymerase as a target of COVID-19. The top 10 ligands selected on the basis of their higher docking scored were screened further ADMET and drug-likeness properties are interpreted based on marginal values compared with the resultant value.

We analysed the pharmacokinetics like blood brain barrier, plasma protein binding and human intestinal absorption. The computational BBB value corresponds to the weather the compound passes across the blood brain barrier. The acceptable BBB value range is between 2 to 0.1 here all the top ten ligands have under this ideal range. The plasma protein binding level provides the information of drug concentration and transport across the cell membrane. Higher the value of PPB gives the way of absorption of the drug; here all the ligands exhibit good binding capacity exceptRaltegravir and AZD7986. Prediction of HIA (Human Intestinal Absorption) drugs is very important to identify the potential inhibitor of proteins. The range of well absorbed compounds is 70-100%. Here all the compounds exhibit good absorption except Remdesivir. Except for Remdesivir, Nelfinavir, Saquinavir, and Setrobuvir, all of the drugs examined have a molecular weight in the range of 381.9 to 457.4g/mol (<500).The present investigation predicts all the highest best binding compounds have a number of rotatable bonds less than 15 except saquinavir. They have less than 5 hydrogen bond donors. Besides, the number of hydrogen bond concepts (O and H) predicts all the compounds are less than except Remdesivir. Permeability coefficients (logP) of the compounds were also studied and found that all ligands showed value of logP less than 5 except (Table1).

3.4 Protein Ligand Integration and Visualization

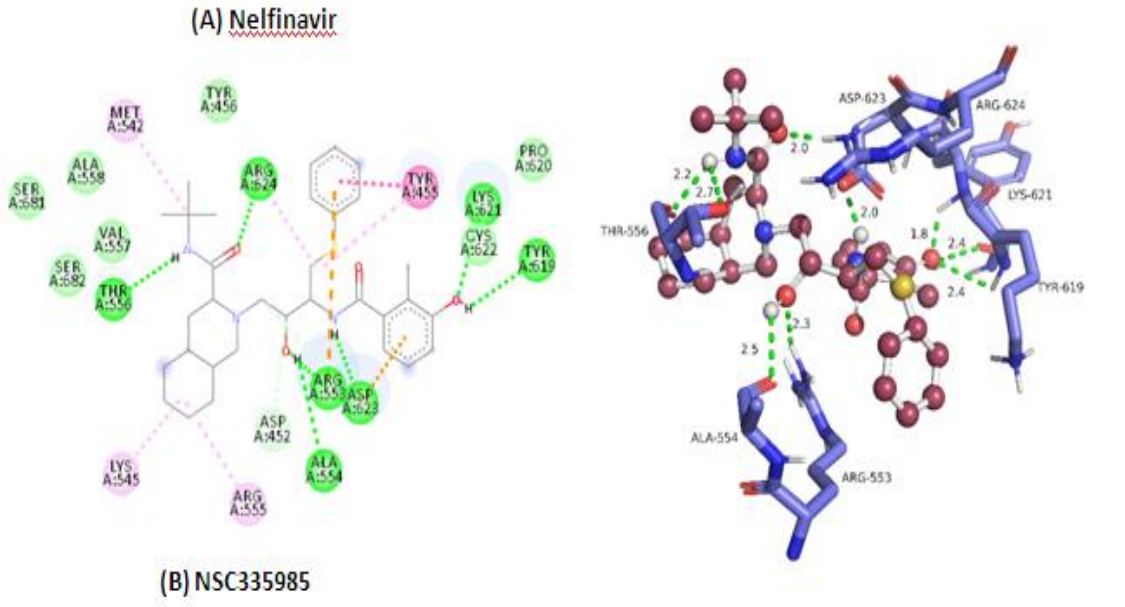
There are more than 10 synthetic ligands which showed good activity against RNA dependent RNA polymerase functional sties. Depending on the higher docking score, ADMET and drug likeness prediction top 5 ligands were selected nelfinavir, NSC335985, NSC29007, NSC159375, AZD7986 were having lower binding scores than other ligands, which reveals promising binding affinity towards the active site of coronavirus RdRp. **Fig 6**shows the minimum docked poses of ligand with the target protein RdRp along with their corresponding 2 D and 3D interaction plots within the active site of Coronavirus RNA dependent RNA polymerase. The reference molecule Remdesivir against RdRp shows interaction with the several residues form 3 H-bond with Ar553, Arg624 and Ser682 and yield the binding energy (-6.08 kcal/mol). Out of the 5 compounds, Nelfinavir exhibited the best docked score (10.06 Kcal/mol) with RdRpof coronavirus and formed H-bond to Arg553, Ala554, Thr556, Tyr619, Asp623 and Arg624. NSC335985 exhibited (9.49kcal/mol) and formed H-bond to Lys545, Arg553, Arg555, Thr556, Asp623 and Ser682. NSC29007 exhibited (-9.40kcal/mol) and formed H-bond to Tyr456, Arg553, Thr556 and Ser682. NSC159375 exhibited (-9.19kcal/mol) and formed H-bond to Asp452, Thr556 and Arg624. AZD7986 exhibited (-8.77kcal/mol) and formed H-bond to Arg553, Arg555, Asp623 and Lys676.The top five ligands and standard ligands with bonded and non-bonded interaction of amino acid present in the active site of protein RdRp are mentioned in the Table 2.

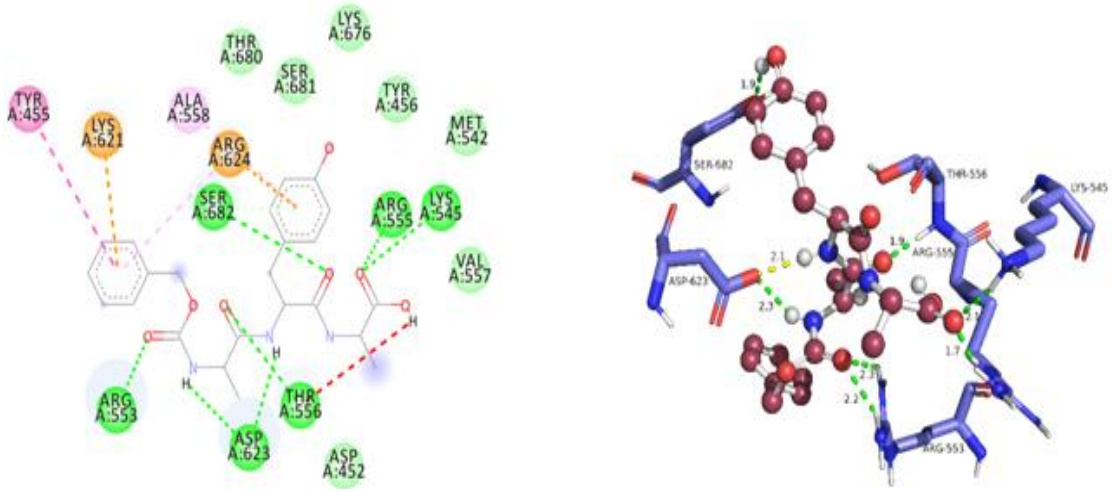
Table 1. ADME properties and Lipinski's rule prediction of top ten synthetic ligands interactive with the nsp12 protein

Sl no	Molecules	Binding Energy (kcal/mol)	ADME properties			Lipinski's 5 rules				
			BBB	HIA	PPB	HBD	HBA	RB	M.W	log P
1	Remdesivir	-6.08	0.045	53.50	81.26	4	12	14	602.6	1.50
2	Nelfinavir	-10.06	1.635	92.67	84.47	4	5	12	567.8	4.33
3	NSC335985	-9.49	0.043	74.25	84.13	5	7	14	457.4	2.38
4	NSC29007	-9.40	0.012	94.93	100.00	2	6	7	429.4	2.42
5	NSC159375	-9.19	0.044	92.51	95.68	3	5	8	424.49	1.95
6	AZD7986	-8.77	0.024	95.65	51.86	2	6	6	420.42	3.21

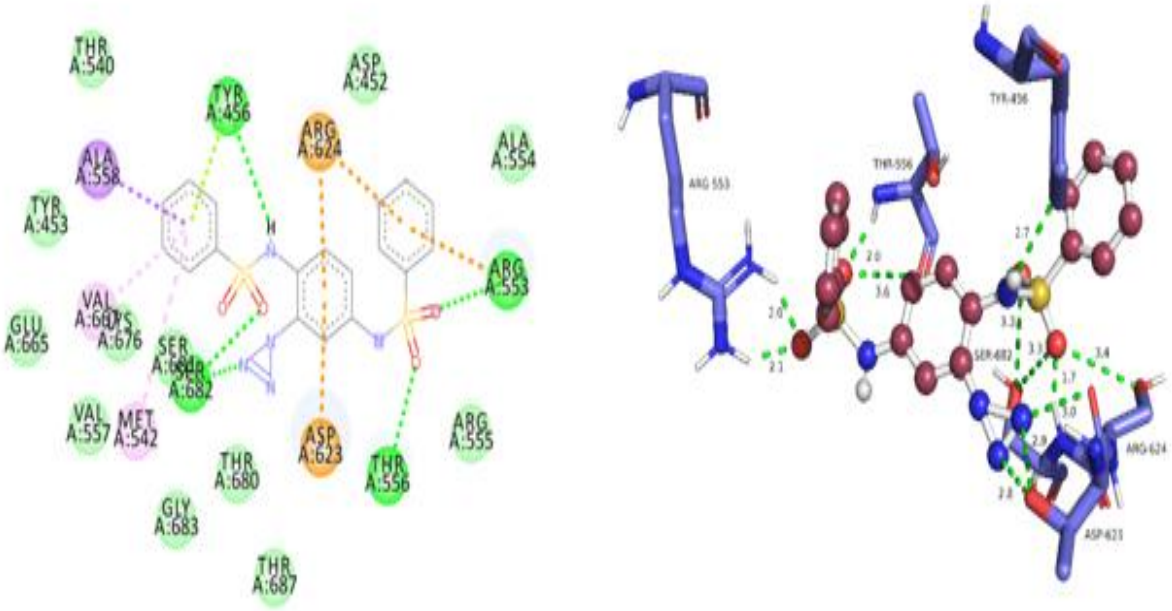
Sl no	Molecules	Binding Energy (kcal/mol)	ADME properties			Lipinski's 5 rules				
			BBB	HIA	PPB	HBD	HBA	RB	M.W	log P
7	Raltegravir	-8.59	0.0430	76.78	48.76	3	6	8	444.40	1.46
8	Saquinavir	-8.47	0.120	89.89	77.75	5	7	16	670.8	3.17
9	NSC337571	-8.43	0.177	90.44	83.92	3	5	11	384.4	2.48
10	Setrobuvir	-8.33	0.021	94.72	99.41	3	8	5	560.6	2.21
11	Azelastine	-8.18	0.295	98.56	82.75	0	3	3	381.9	4.4

**BBB:Blood Brain Barrier Penetration, high absorption to CNS >2.0, middle absorption to CNS 2.0 ~ 0.1, Low absorption to CNS <0.1*HIA:Human Intestinal Absorption, poorly absorbed compound=0~20%, moderately absorbed compounds= 20~ 70%, well absorbed compounds 70~100%*PPB:Plasma Protein Binding, Chemicals strongly bound >90%, Chemicals weakly bound <90%*HBD:Hydrogen Bond Donor (<5), *HBA:Hydrogen Bond Acceptor (<10), *RB:Rotatable bonds (<15), *M. W:Molecular Weight (<500g/mol). * Log P: Partition coefficient*

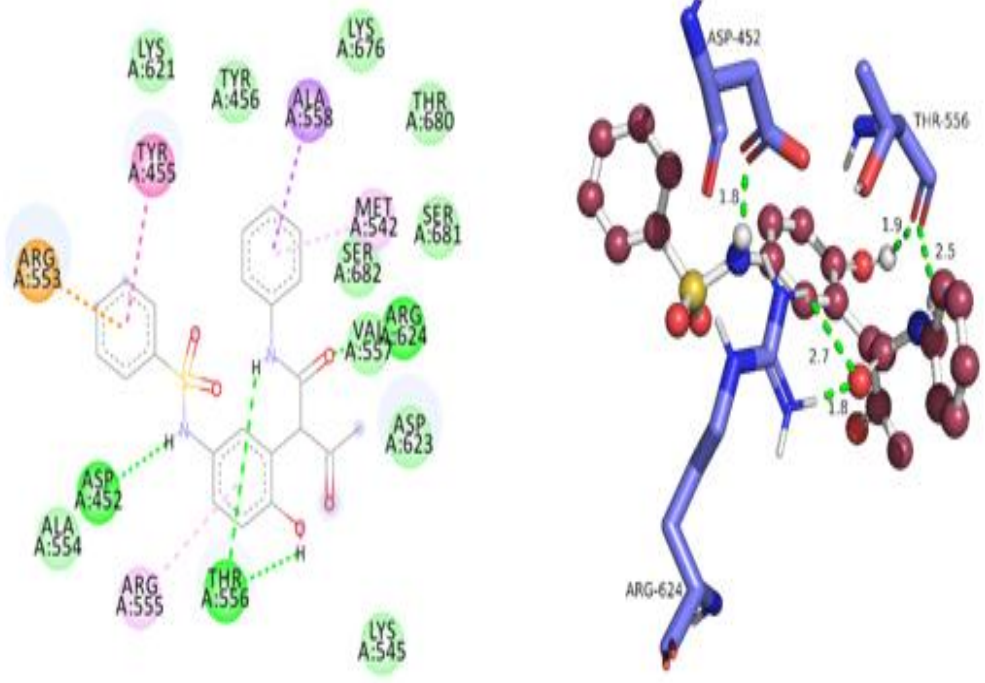




(C) NSC29007



(D) NSC159375



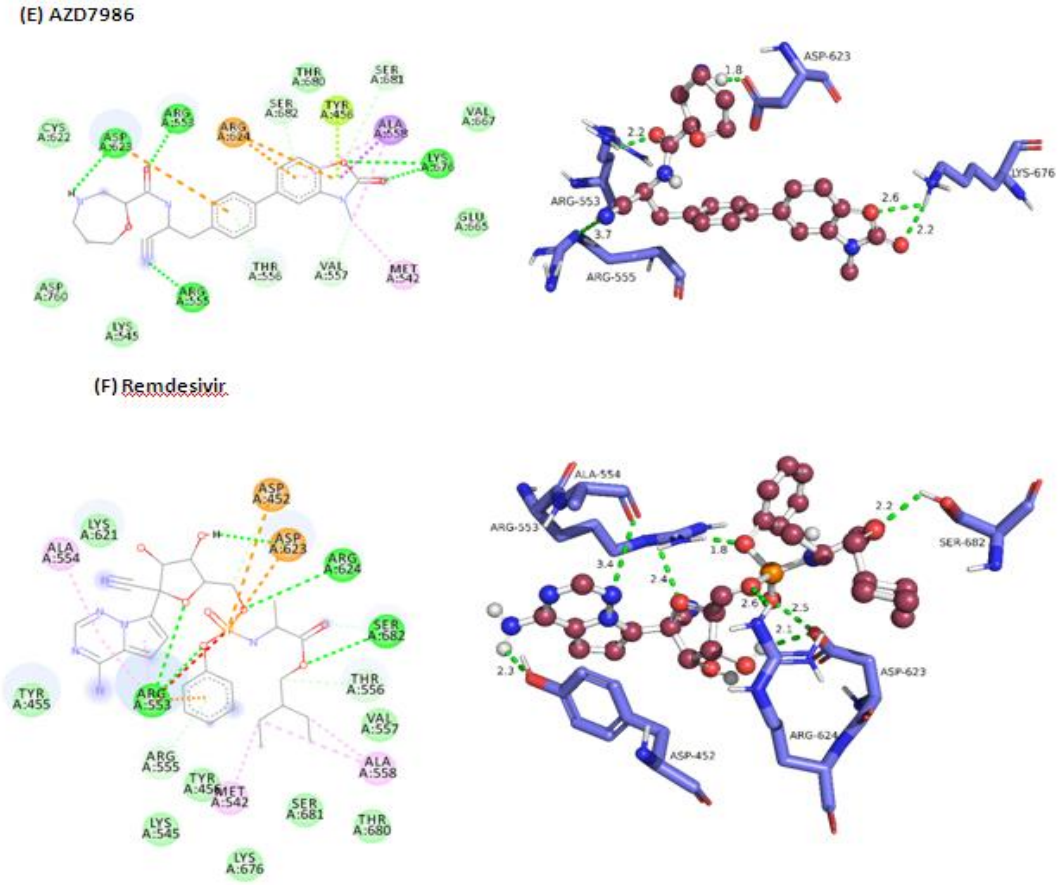


Fig. 6. Shows the 2D and 3D interaction of ligand with the target protein RdRp docked using AutoDock 4.2.6 3D interaction visualized by using PyMol software and the 2D interaction visualized by using Discovery Studio Visualizer software (A)Nelfinavir (B)NSC335985 (C) NSC29007 (D) NSC159375 (E) AZD7986 (F) Remdesivir the ligand represented in ball and stick format in raspberry colour, the interacting amino acid residues represented in stick format in blue colour, the bond length between the amino acid and ligand are represented in green dashed lines

Table 2. Molecular docking analysis to find out the binding sites of selected synthetic inhibitors on RdRp (RNA dependent RNA polymerase)

Sl. No	Compound	Molecular Formula	Binding Energy (kcal/mol)	H-Bonded interaction	Non-bonded interaction (van der Waals)
1	Nelfinavir	$C_{32}H_{45}N_3O_4S$	-10.06	Arg553, Ala554, Thr556, Tyr619, Asp623, Arg624	Tyr456, Val557, Ala558, Pro620, Ser681, Ser682
2	NSC335985	$C_{23}H_{27}N_3O_7$	-9.49	Lys545, Arg553, Arg555, Thr556, Asp623, Ser682	Asp452, Tyr456, Met542, Val557, Lys676, Thr680, Ser681
3	NSC29007	$C_{18}H_{15}N_5O_4S_2$	-9.40	Tyr456, Arg553, Thr556, Ser682	Asp452, Tyr453, Thr540, Ala554, Arg555, Val557, Glu665, Lys676, Thr680, Ser681,

Sl. No	Compound	Molecular Formula	Binding Energy (kcal/mol)	H-Bonded interaction	Non-bonded interaction (van der Waals)
4	NSC159375	$C_{22}H_{20}N_2O_5S$	-9.19	Asp452, Thr556, Arg624	Gly683, Thr687 Tyr456, Lys545, Ala554, Val557, Lys621, Asp623, Lys676, Thr680, Ser681, Ser682
5	AZD7986	$C_{23}H_{24}N_4O_4$	-8.77	Arg553, Arg555, Asp623, Lys676	Lys545, Cys622, Glu665, Val667, Thr680, Asp760
6	Standard: Remdesivir	$C_{27}H_{35}N_6O_8P$	-6.08	Arg553, Arg624, Ser682	Tyr455, Tyr456, Lys545, Val557, Lys621, Lys676, Thr680, Ser681

Nelfinavir showed the highest binding energy those of among all other ligands involved in study i.e., -10.06kcal/mol for the active site of RNA dependent RNA polymerase and it also accept the ADMET and drug likeness prediction. Hence the present study suggests that nelfinavir have the potential ability to act as therapeutic agent against coronavirus multiplication as well as infection. This preliminary study may be contributory towards the anti-epidemic efforts against the newly emerged COVID-19and may help to shortlist the antiviral drugs against COVID-19 for clinical trials.

4. CONCLUSIONS

Coronavirus (CoVs) have induced a main outbreak of human fatal pneumonia due to the fact that the start of the twenty-first century. There is no specific antiviral drug or treatment till date. In summary, we performed the molecular docking studies of synthetic drugs chosen by literature survey against anti-MERS, Anti-HIV, Anti-malarial to inhibit the protein RNA-dependent RNA polymerase and compared the docking score with the standard drug Remdesivirpretended to be a temporary therapeutic drug for COVID-19. Our study revealed all the tested synthetic drugs showed highest docking score compared to Standard ligand Remdesivir. Out of fifty compounds docked, the ten compounds with high binding energies were selected for further drug-likeness and pharmacokinetic prediction. Out of ten compounds top five Compounds were selected which showed best binding energy, ADMET and drug likeness properties nelfinavir>NSC335985 > NSC29007> NSC159375> AZD7986. Among them Nelfinavir has the highest binding affinity (-10.06 kcal/mol) to COVID-19 RNA dependent RNA polymerase with good drug likeness and pharmacokinetics properties. Further research is urgently required to investigate the potential antiviral drug uses of these drugs for designing and developing an effective medicine against COVID-19.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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