Repurposing 57 well-known drugs for three COVID-19 targets: Mpro, Spike, RdRp

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Abstract— The pandemic that we are currently living through, caused by SARS COVID-19, changed the way we perceive deadly diseases along with our comprehension of efficacious drugs. In this paper, we compare 57 repurposable drugs from different categories like anti-inflammatory, anticancer, anticoagulant, antiviral, anti-parasitic, antidepressant, Parkinson's disease drugs, and discontinued drugs, to identify the best drugs with strongest binding affinities, that can be considered for treating COVID-19. We identified three target proteins- Main protease (PDB ID: 6LU7), Spike Glycoprotein with human receptor ACE2 (PDB ID: 6M0J), and RNA-dependent RNA polymerase (RdRp) in complex with Remdesivir (PDB ID: 7BV2) which are responsible for transcription, entrance into host's cell and viral replication respectively. We used AutoDock Vina for docking, and based our results on the binding affinity and hydrogen bond interactions. We shortlisted 15 drugs- Vilazodone, Lopinavir, Ritonavir, Darunavir, Selinexor, Etoposide, Nintedanib, Methylprednisolone, Hydrocortisone, Tolcapone, Apixaban, Rivaroxaban, Dabigatran, Betrixaban, and Amprenavir- that showcased comparable or higher affinity than Remdesivir with all of our three target proteins, and recommend these for further studies.

Keywords—Mpro, Spike, RdRp, repurposing, Remdesivir, anticoagulant, anticancer

I. INTRODUCTION

When the World Health Organization announced COVID-19 as a pandemic on 11th March 2020, there was little known about its structure or pathogenesis, except that it is similar to the severe acute respiratory syndrome coronavirus which was found in China in 2002. After a year of living through the pandemic, with five vaccines currently in use, and more underway, we remain almost equally helpless as the virus continues to mutate and spread exceedingly rapidly. The news is filled with the world undergoing destruction caused by the coronavirus. Exponential increase of people affected,

lockdowns, shortage of vaccines, shortage of hospital beds, people suffering from breathlessness and waiting for the now almost non-existent expensive oxygen cylinders, and the blanket of grief shrouding the gray world. Working from home, wearing masks, social distancing, and constant paranoia is our new normal. Through it all, our one shining beacon of hope, Remdesivir burns brightly. But Remdesivir works by decreasing the effects of the virus only in severe cases of the COVID-19 and has no effect on mild to moderate cases. Only a fully vaccinated population can be declared healthy and safe. Africa only vaccinated 1% of their entire population. New research now predicts that coronavirus could be affected by seasons like the influenza virus, which peaks during winters [1]. Their research, which is based on the epidemiological data of the virus, hypothesized that the virus could make a regular appearance every winter and recede during the summers. Recently, Pfizer released a statement declaring the need for a third dose of the vaccine within 12 months of the second dose to reach optimum immunity. This prolongs the already steep road to normalcy and opens up new opportunities for the virus to attack even the vaccinated population.

Drug Repurposing is a cost and time effective strategy to combat the disease. While vaccines take several months to develop, and then undergo numerous testing stages, drug repurposing proves to be a safe alternative. Repurposing or Repositioning known drugs with known side-effects and dosages drastically reduces the time period of treating a disease. Commonly available drugs which can decrease the severity of the virus can help in tipping the scales of this pandemic.

Presently, there are three vital proteins that most in silico studies are based on [2]. The main protease or 3CL is responsible for transcription and viral replication, the spike protein plays the significant role of binding to the human ACE2 receptor which guarantees it entry to the host's cell, and RNA-dependent RNA polymerase (RdRp) or non-structural protein 12 (nsp12). The RNA-dependent RNA polymerase protein or non-structural protein 12 is vital for the viral replication once it enters the host's cell. Hence, it is imperative to find suitable inhibitors to this protein which works together with other non-structural proteins such as nsp7 and nsp8 to achieve replication. Remdesivir is our reference drug since it is the only approved drug for treating COVID-19 by the FDA.

2. MATERIALS AND METHODS

2.1. TARGETS

2.1.1. Main Protease or Mpro

The coronavirus 2019 main protease or Mpro became the most popular target for numerous drug repurposing studies due to its vital role in transcription and viral replication [3]. The main protease contains two identical subunits which create two active sites. Its cleavage site is located after a glutamine residue, which is exclusive to the protease and hence, does not interfere with the host cell interactions, unlike the papain-like protease or PLpro [4]. The PDB ID 6LU7 which represents the crystal structure of main protease formed using X-ray diffraction at 2.16 A resolution, is in complex with inhinitor N3 at one of the active sites. The 3C-like proteinase cleaves the polyproteins pp1a and pp1b, giving rise to functional proteins such as nsp12, nsp7 and nsp8 which are responsible for viral replication inside the host cell. The presence of inhibitor at the binding site allows performing ligand centered docking, centered on the inhibitor N3. Remdesivir, our reference drug, formed H-bonds with residues GLY143, CYS145, and GLU166.

2.1.2. RNA-dependent RNA polymerase

The non-structural proteins of the coronavirus 2 are responsible for transcription and replication of the virus [5]. Nsp12 or RdRp, in complex with nsp7 and nsp8 help in improving the processivity. The PDB ID 7BV2 represents RdRp or nsp12 in complex with its other non-structural proteins nsp7 and nsp8 with triphosphate form of of Remdesivir bound to the active site. The structure has been determined by the Electron Microscopy method at 2.50 A resolution. The structure of RdRp is similar to that of SARS-CoV, and consists of an nsp8 subunit, nsp7-nsp8 heterodimer and a nsp12 core unit [6]. Since the RNA-dependent RNA polymerase has highly conserved active catalytic motifs, it makes for a popular drug target for antiviral inhibitors. The presence of Remdesivir in the active site makes it easy to determine the binding box and to execute docking studies based on the ligand. Superimposition of Remdesivir with the structure bound Remdesivir validates the chosen binding pocket. Remdesivir forms H-bonds with residues ASP760, ARG553, and ARG555.

2.1.3. Spike Glycoprotein

The virus that is currently causing the pandemic achieved its moniker "coronavirus" due to its crown-like spike glycoproteins. The spike protein is responsible for binding to the human

receptor Angiotensin- converting enzyme 2, which grants it entry into the host's cell. The spike is a homotrimeric glycoprotein consisting of S1 and S2 subunits in individual monomers [7]. The PDB ID 6M0J represents the crystal structure of spike receptor binding domain bound with human receptor ACE2 using X-ray diffraction at 2.45 A resolution. Lack of an inhibitor prompts the implementation of blind docking with Remdesivir forming the H-bonds PHE40, SER44, ALA348, ASP350, ASP382 and ASN394.

2.2.   LIGANDS

The drug candidates from ten categories: Anti-HIV drugs, CNS drugs, Antiviral drugs, Anticancer drugs, Anti-parasitic drugs, Anti-inflammatory drugs, Parkinson's disease drugs, Anti-depressants, Anticoagulants and few discontinued drugs were selected through an extensive literature survey and validated using the CORDITE (https://cordite.mathematik.uni-marburg.de/#/) database. BIOVIA Draw was used to draw the 2D structure of these ligands which were converted to 3 dimensional PDB format using Frog2 software, which is inclusive of energy minimization.

Antiviral drugs are the most common repurposed drugs to treat covid-19. Remdesivir, an FDA approved drug, is the most popular repurposed drug for COVID-19 with numerous in vitro, in silico, and in vivo studies proving its efficacy against the coronavirus 2. Many countries are using it to reduce the severity of the disease. Remdesivir or GS-5734, is an antiviral drug originally meant for Hepatitis C, then repurposed for treating Ebola, and now repurposed again to treat COVID-19. Lopinavir/ Ritonavir and Favipiravir are also other widely used repurposed drugs for treating the disease [8-13]. While these drugs were used by medical practitioners in the early stages, they have now been discontinued for treating COVID-19 due to the lack of efficacy. Anti-cancer drugs are also being considered for drug repurposing strategies since the purpose of those drugs also target controlling the host environment, reducing inflammation, and inhibiting cell proliferation [14]. In using corticosteroids for treating the disease, existing in vivo research supports using Budesonide [16], Dexamethasone and Methylprednisolone [17] for further randomized clinical trials to affirm the drawn conclusions. Anti-parasitic drug, Ivermectin, which garnered a wide amount of speculation over its use in treating the disease, has proven to be effective in preventing the replication of the virus in in vitro, but requires further in vivo studies to ascertain its efficacy [18]. Chloroquine and Hydroxychloroquine, on the other hand, have been in use to treat patients during the early stages of the pandemic, before they were prohibited due to low efficacy and strong side-effects [19]. Anticoagulants are required to reduce the complications caused by the disease like

thrombosis, but no research has been published yet which shows the efficiency of anticoagulants in inhibiting the viral proteins [20]. There are several clinical trials currently underway and few which already concluded that the antidepressants Fluvoxamine and Fluoxetine aid in reducing the inflammation caused by the disease and limit the deterioration of patients affected [21], though official approval is required for these drugs to be considered as a potential treatment option for the disease. The figure 1 below lists the flowchart of methodology.

2.3. HARDWARE AND SOFTWARE SPECIFICATIONS

The research has been conducted with the following system specifications. Processor: Intel ® Core ™ i5-6400 CPU @ 2.70 GHz, Installed RAM: 4.00 GB, System type: 64-bit operating system, x64-based processor. The Windows specifications are Edition: Windows 10 pro, Version: 1909.

BIOVIA draw was implemented for drawing the 2D structures of fifty-seven ligands. Frog2 software converts the drawn 2D structures of these ligands to 3D with built-in energy minimization. Prediction of binding pockets of targets is done using PrankWeb and CASTp software. AutoDock Vina is required for the docking process, with PMV tools 1.6 showing the graphical representation. BIOVIA Discovery Studio is used to visualize the docked conformation of the ligand in the binding site as well as to analyze features like H-bonds.
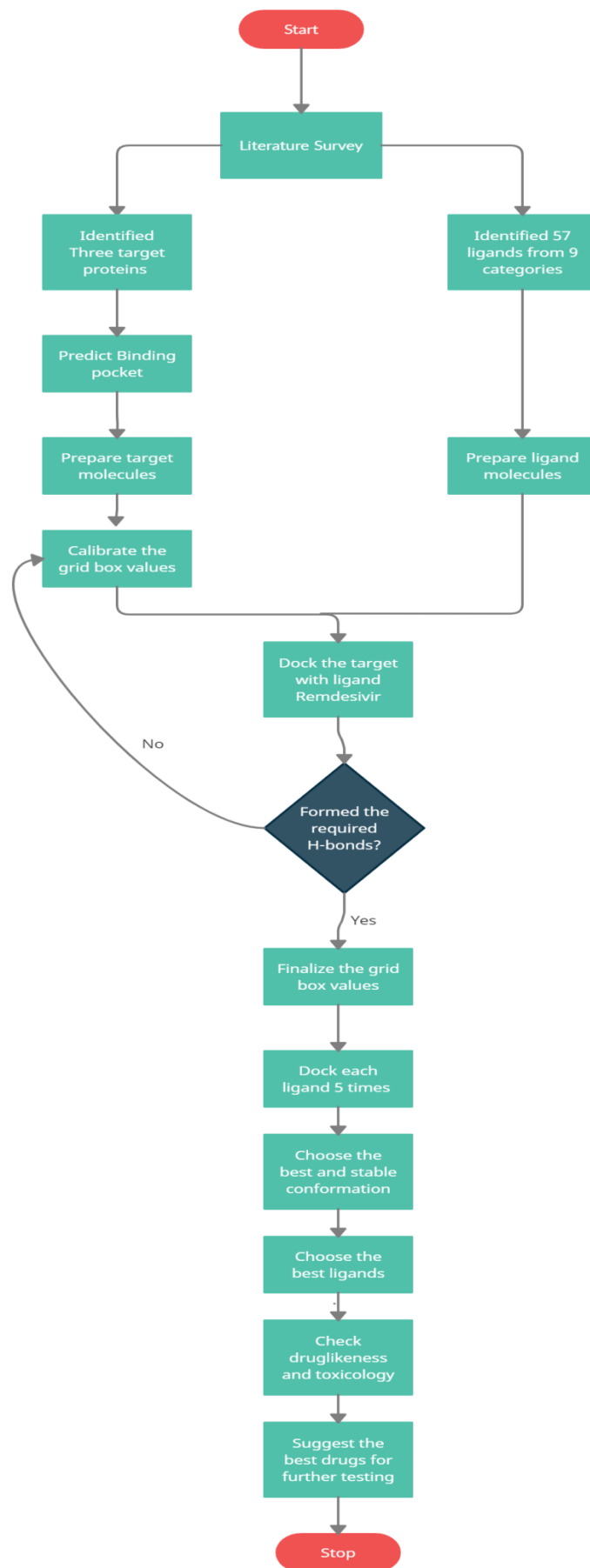
Figure 1: Flowchart of methodology

2.4. DOCKING USING AUTODOCK VINA

2.4.1. Preparation of target molecules

We downloaded the PDB structure of the target proteins 6LU7, 6M0J, and 7BV2 from Protein Data Bank. Minimized the energy of the proteins to achieve stable conformations. Deleted all water molecules except the ones in the binding pocket. According to recent studies, polarized water molecules in binding pockets aid in increasing the binding affinity of the ligand rather than reducing it, as they act as part of the protein and influence the ligand binding conformation [22]. We then added all hydrogens with bond order and Kollman charges. Since crystal files generally lack hydrogen atoms, adding them is necessary to optimize the system. Save the files in PDBQT format.

2.4.2. Preparation of Ligand Molecule

Convert the drawn 2D structure of ligand in SMILES or Mol format to PDB using Frog2 software with in-built energy minimization. Frog2 also adds the hydrogens inclusively, so just remove water ions present, if any. Next, add stereo chemical information, if it lacks stereoisomers, followed by adding Gasteiger charges. Go to the ligand option of ADT tools, and choose the ligand. Adjust the rotatable bonds as necessary (<10 is preferable), and save the ligand in PDBQT format.

2.4.3. Choosing Grid parameters

The receptor is to be rigid and the ligand, flexible. Select the macromolecule and adjust the grid box values appropriately to calculate the surface area. This helps in analyzing the binding pockets of the receptor for docking. Since RdRp (7BV2) and Mpro (6LU7) have crystal structures with a ligand and inhibitor complex respectively, we set the binding box centered on them and superimposed our docked output with the respective ligand to choose the optimum grid box values. The grid box values of 7BV2 are x-center=100.84, y-center=92.664, z-center= 105.585, and x-points=24, y-points=12, and z-points=10, the spacing set to 1 A. The center grid box values of 6LU7 are x-center=-10.749, y-center=12.46, z-center= 68.91, and the sizes are x-points=24, y-points=24, and z-points=22, the spacing set to 1 A. Due to the lack of crystal structures of spike glycoprotein with ligands, we performed blind docking for the target protein 6M0J. Blind docking is to choose the grid values in such a way as to cover the entirety of the protein. The grid box values chosen for 6M0J are x-center=-23.088, y-center=18.676, z-center= -27.106, and x-points=64, y-points=66, and z-points=72, the spacing set to 1 A [10].

2.4.4. Evaluation of Results

Dock each ligand multiple times to reach a stable conformation. Select the stable conformation with lowest binding affinity and analyze the H-bonds.

3. RESULTS

3.1. RNA-dependent RNA polymerase

The target molecule 7BV2, which is the protein RNA-dependent RNA polymerase (RdRp), in complex with Remdesivir, has the binding pocket with residues ARG555, TRP617, ASP618, TYR619, LYS621, CYS622, ASP623, THR680, SER682, ASP684, THR687, ALA688, ASN691, SER759, ASP760, ASP761, LYS798, THRP800, and GLU811 . Since the crystal is in complex with the ligand Remdesivir, after deleting the heteroatom, ligand-based docking was performed and the resulting conformations were superimposed with the molecule's Remdesivir to confirm the binding pocket. Remdesivir bound to RdRp in the binding pocket with a binding affinity of -7.4 kcal/mol and made the following H-bonds: ASP760, ARG553, ARG555, and SER682, which is taken as the reference. 7BV2 exhibited highest binding affinity to Etoposide, an antineoplastic drug used to treat leukemia, ovarian cancer, lung cancer, testicular cancer and lymphoma. It exhibited a binding affinity of -8.4 kcal/mol with 7BV2 and made H-bonds with residues ARG555 and ASN691. Figure 2 shows the docked result of Etoposide with 7BV2 visualized using BIOVIA Discovery Studio. Dabigatran exhibited the binding affinity -8.2 kcal/mol, follows Etoposide. 7BV2 showed the least binding affinity with Amantadine at -4.6 kcal/mol. It also showed low binding affinities with Pramiprexole, Rasagiline, and Cyamemazine- as proved by its lack of H-bonds. 7BV2 bound well to anticoagulants and anti-cancer drugs in general, while Parkinson's disease drugs displayed low affinity towards 7BV2.

3.2. Spike Glycoprotein

6M0J, which is the spike glycoprotein in complex with ACE2, has the binding pocket PHE40, THR347, ALA348, ASP350, GLU375, HIS378, ASP382, TYR385, ASN394, and HIS 401. Spike protein docked with Remdesivir has a binding affinity of -7.5 kcal/mol and made H-bonds with the residues PHE40, SER44, ALA348, ASP350, ASP382, and ASN394. 6M0J exhibited highest binding affinity to Elbasvir (anti-viral) at -11.6 kcal/mol, and made H-bonds with the residues TRP69,

ASP350, HIS374, and SER409. Figure 3 shows the docked result of Elbasvir with 6M0J visualized using BIOVIA Discovery Studio.
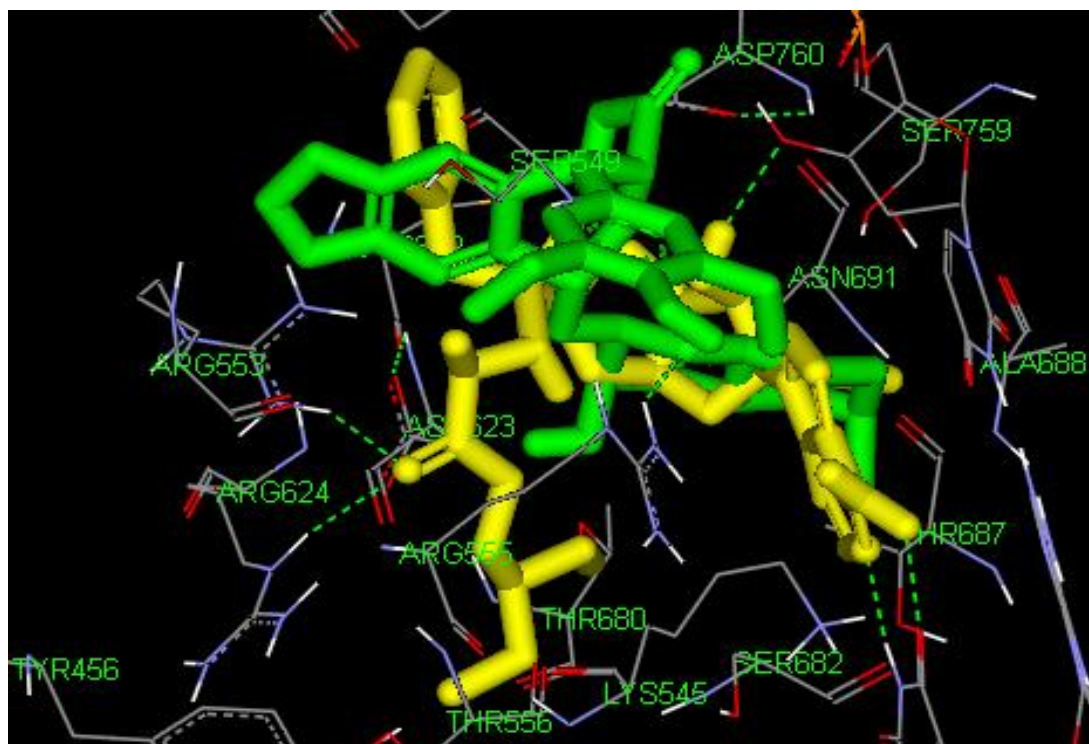

Figure 2: Docked result of Etoposide (Green) with 7BV2 (RdRp), superimposed with Remdesivir (yellow). H-bonds are visualized as dotted green lines using Discovery Studio.

Vilazodone , Bromocriptine (Parkinson's disease drug), Lopinavir (antiviral), and Selinexor (anticancer drug) expressed the binding affinities -10.0, -9.5, -9.2, and -9.2 kcal/mol respectively. 6M0J showed the least binding affinity with Amantadine at -4.9 kcal/mol, as proven by the lack of H-bonds. It also showed low binding affinities with Levamisole and Favipiravir- which wasn't docked at the required binding pocket. Discontinued drugs Telaprevir and Amprenavir also showed promising results with binding affinities -8.5 and -8.1 kcal/mol respectively. 6M0J bound well to anticoagulants, and anti-cancer drugs in general while Parkisnon's disease drugs displayed low affinity towards 6M0J.

3.3. Main Protease
Main protease or Mpro represented by the PDB ID 6LU7 has the binding pocket THR25, THR26, LEU27, HIS41, MET49, PHE140, LEU141, ASN142, GLY143, SER144, CYS145, HIS163, HIS164, MET165, GLU166, ASP187, ARG188, and GLN189. When docked with Remdesivir, H-bonds were created with the residues THR24, THR25, THR26, CYS44, THR45, SER46, ASN142,

GLY143, SER144, CYS145, and HIS164. Mpro has the highest binding affinity with Vilazodone at -8.8 kcal/mol and made H-bonds with the residues SER46, THR25, and THR45. Figure 4 shows the docked result of Vilazodone with 6LU7 visualized using BIOVIA Discovery Studio. Selinexor, Etoposide and Betrixaban, exhibited higher affinities than Remdesivir at -8.4, -8.4, and -8.3 kcal/mol respectively. Hydrocortisone, Bromocriptine, Methylprednisolone, Lopinavir, Darunavir, Nintedanib, Rivaroxaban, and Amprenavir showed comparable affinity with Remdesivir at -8.1, -8.1, -8.0, -7.9, -7.9, -7.8, -7.8, -7.7, and -7.7 kcal/mol respectively. Amantadine showed the least binding affinity with 6LU7 at -4.8 kcal/mol. Anticoagulants bound well to 6LU7 while Parkinson's disease drugs showed least binding affinities towards the main protease. Table 1 showcases the binding affinities of the 57 drugs with respective target proteins. The hydrogen bonds made by each ligand with the protein are displayed in Table 2. Docking results of best ligands for each protein are included in supplementary files.
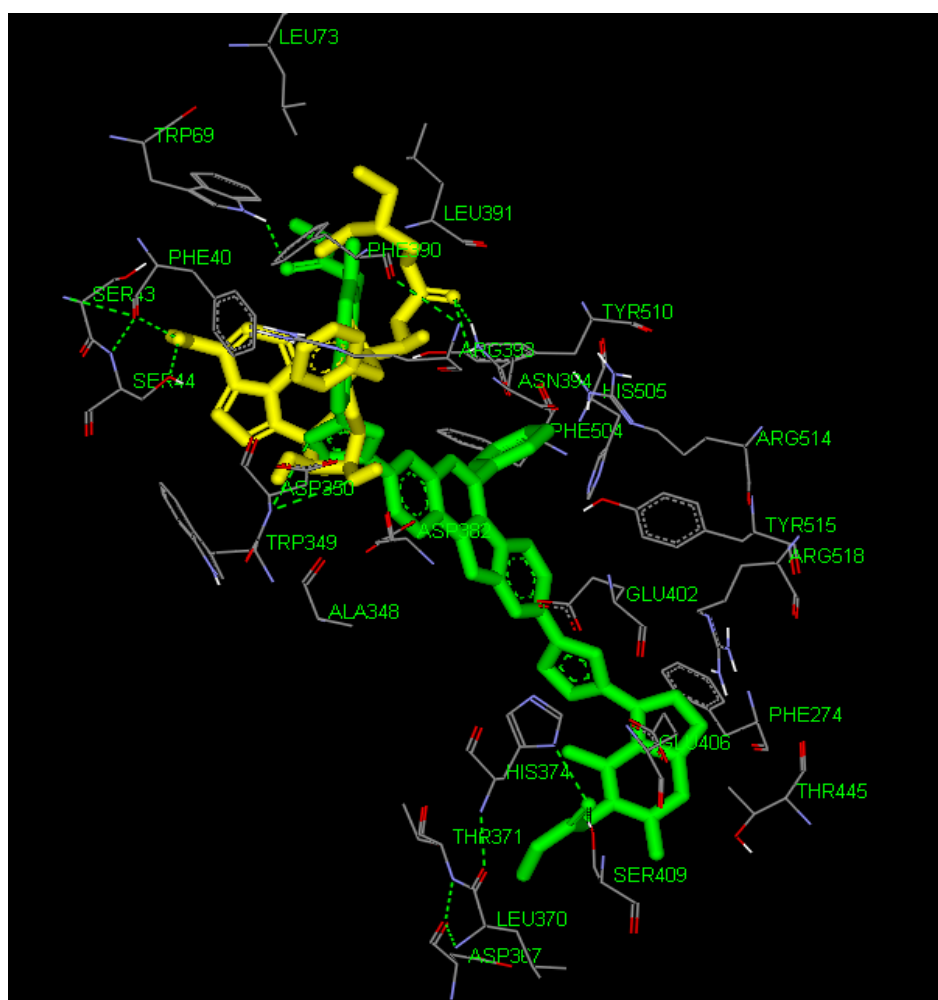
Figure 3: Docked result of Elbasvir (Green) with 6M0J (Spike), superimposed with Remdesivir (yellow). H-bonds are visualized as dotted green lines using Discovery Studio.
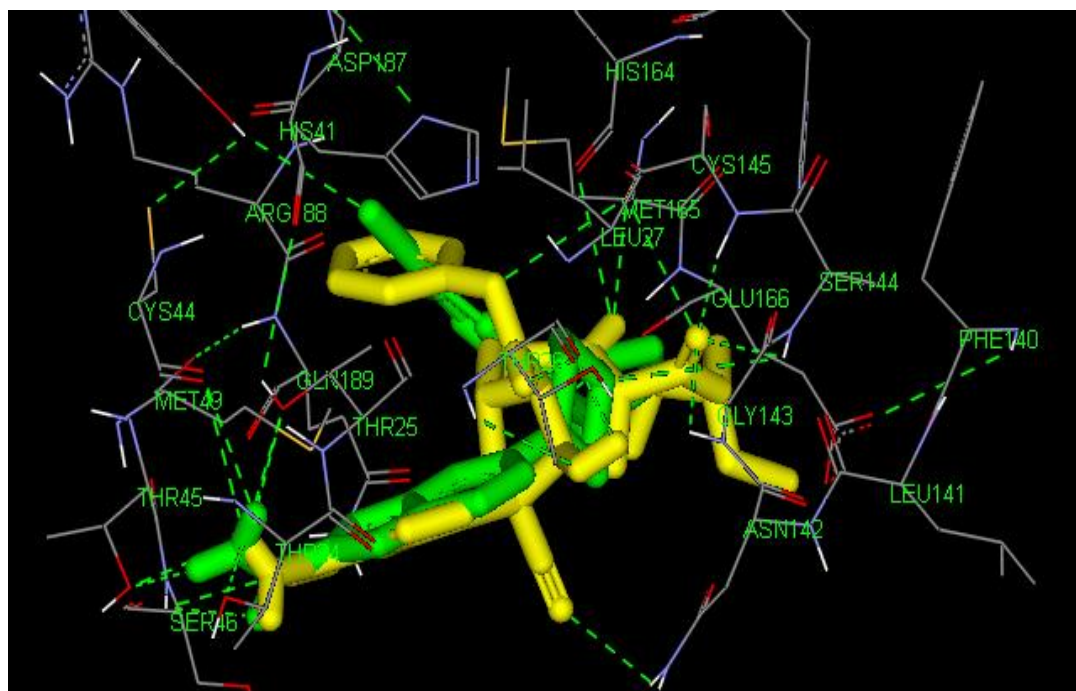
Figure 4: Docked result of Vilazodone (Green) with 6LU7 (Mpro), superimposed with Remdesivir (yellow). H-bonds are visualized as dotted green lines using Discovery Studio.

Drug	BA of 7BV2 kcal/mol	BA of 6M0J kcal/mol	BA of 6LU7 kcal/mol
Reference-Remdesivir	-7.4	-7.5	-8.1
Anti-HIV agents			
Etravirine	-6.5	-8.7	-7.5
Dapivirine	-7.1	-8.3	-7.1
Rilpivirine	-6.8	-8.8	-7.4
Lersivirine	-5.8	-6.3	-6.2
CNS Drugs			
Escitalopram	-5.6	-6.9	-6.3
Vilazodone	-7.6	-10.0	-8.8
Periciazine	-6.1	-8.0	-7.5
Cyamemazine	-5.5	-6.4	-6.5
Zaleplon	-6.8	-7.4	-7.1
Donitriptan	-7.5	-8.1	-7.3
Antiviral drugs			
Lopinavir	-7.6	-9.2	-7.9

Ritonavir	-7.1	-8.4	-7.5
Favipiravir	-5.7	-5.9	-5.1
Ribavirin	-6.8	-6.8	-6.4
Darunavir	-7.9	-7.9	-7.9
Arbidol	-6.2	-7.3	-6.5
Elbasvir	-5.7	-11.6	-7.5
Sofosbuvir	-7.8	-7.2	-7.2
Galidesivir	-6.6	-6.7	-6.9
Anti-cancer Drugs			
Thalidomide	-7.1	-6.8	-6.7
Selinexor	-8.0	-9.2	-8.4
Etoposide	-8.4	-7.9	-8.4
Nintedanib	-7.4	-8.5	-7.8
Anti-parasitic Drugs			
Ivermectin	-5.7	-8.8	-7.3
Chloroquine	-5.8	-6.1	-5.8
Levamisole	-5.7	-5.9	-5.6
Nitazoxanide	-6.7	-6.7	-6.3
Hydroxychloroquine	-5.8	-6.1	-5.8
Anti-inflammatory drugs			
Budesonide	-6.0	-8.5	-7.1
Dexamethasone	-6.6	-7.8	-7.3
Methylprednisolone	-7.1	-7.9	-8.0
Prednisone	-6.9	-7.8	-7.1
Hydrocortisone	-6.9	-7.4	-8.1
Prednisolone	-6.9	-7.5	-7.3
Parkinson's Disease Drugs			
Amantadine	-4.6	-4.9	-4.8
Levodopa	-5.8	-6.3	-5.7
Entacapone	-5.9	-6.2	-6.3

Tolcapone	-7.2	-7.1	-7.6
Bromocriptine	-5.7	-9.5	-8.1
Ropinirole	-5.6	-6.3	-5.6
Pramiprexole	-4.8	-5.3	-5.5
Rotigotine	-5.3	-6.0	-6.1
Selegiline	-5.2	-5.7	-5.1
Rasagiline	-4.9	-6.1	-5.4
Anti-Depressants			
Fluvoxamine	-6.3	-6.1	-5.9
Fluoxetine	-6.7	-7.0	-6.6
Anti-Coagulants			
Apixaban	-8.0	-7.8	-7.5
Edoxaban	-7.7	-8.5	-7.3
Rivaroxaban	-7.7	-7.9	-7.8
Dabigatran	-8.2	-8.6	-7.5
Betrixaban	-8.0	-7.9	-8.3
Discontinued Drugs			
Vidarabine	-7.2	-6.7	-6.3
Zalcitabine	-5.9	-6.2	-5.6
Amprenavir	-7.2	-8.1	-7.7
Boceprevir	-6.6	-7.6	-6.8
Telaprevir	-5.7	-8.5	-7.0

Table 1: **Binding affinities of 57 ligands with 7BV2, 6M0J, and 6LU7**

Drug	H-bonds 7BV2	H-Bonds 6M0J	H-bonds 6LU7
Reference-Remdesivir	ASP760	PHE40	THR24
	ARG553	SER44	THR25
	ARG555	ALA348	THR26
	SER682	ASP350	CYS44
		ASP382	THR45
		ASN394	SER46
			ASN142
			GLY143
			SER144

			CYS145
			HIS164
Anti-HIV agents			
Etravirine	ASP760 ASP623	ASP350 ASP382 HIS401 ASN394	GLY143 GLU166 HIS164 THR190
Dapivirine	ASP760	ASP382 ASP350 ARG393 GLU402	GLU166 CYS145
Rilpivirine	ASP760	ASP350 ARG393	GLU166 HIS164 ASP187
Lersivirine	ARG555 CYS622	ASP350 ARG393 ASN394	SER144 GLU166
CNS Drugs			
Escitalopram	ARG555 ASN691	SER47 ARG393 ASN394	THR26 PHE140 GLU166
Vilazodone	SER682 ASP760	ASP350 GLN102	SER46 THR25 THR45
Periciazine	ARG555	VAL343 HIS345	THR190 PHE140 HIS163 GLU166
Cyamemazine	No H-bonds	VAL343 HIS345	NO H-BONDS
Zaleplon	ASN691 ARG553 SER759	ASN394	GLY143 THR26
Donitriptan	ASN691	LYS74	GLY143

	SER759	ASP350	THR25
	LYS621	ASN103	
Antiviral drugs			
Lopinavir	ARG553	ASN394	ASN142
	ARG555	GLU375	GLU166
		ALA348	MET165
			GLN189
			ASN142
			ARG188
Ritonavir	ARG553	ASN394	SER144
	ARG555	TYR385	CYS145
		ASP382	GLU166
			GLN189
			HIS163
			THR26
Favipiravir	ARG555	LYS353	SER144
	SER759	GLY496	CYS145
	ASP760	HIS34	
Ribavirin	ARG555	TRP556	GLU166
		ASN210	HIS164
		ALA396	HIS163
Darunavir	ARG555	ASP350	GLU166
	ASP623	ASN394	THR25
	ASN691		GLY143
			CYS44
			THR24
Arbidol	ARG555	ALA348	NO H-BONDS
Elbasvir	ARG555	TRP69	THR26
	LYS621	ASP350	ALA191
		HIS374	THR26
		SER409	ASN119
Sofosbuvir	ARG553	ASP350	THR26
	ASN691	ARG514	GLN189
	ARG555	ASP382	

Galidesivir	ASP760	ASP382 TYR385 ASN394	SER144 LEU141
Anti-cancer Drugs			
Thalidomide	ARG555 ASN691 ASP760	ASN394	GLY143 GLU166 LEU141
Selinexor	ARG553	ARG393 ASP350	GLY143 THR190 GLN192 GLU166 SER144 HIS163 ASN142
Etoposide	ARG555 ASN691	ALA348	GLY143
Nintedanib	ARG555 ASP623	SER47 ALA348 ASP382 ASN394	GLY143 HIS41
Anti-parasitic Drugs			
Ivermectin	LYS551 ARG555 LYS621 CYS622	ASP350 ASN394	GLY143 THR24
Chloroquine	ASN691	ASP350 HIS401	GLY143 HIS164
Levamisole	ARG555	ASP350	NO H-BONDS
Nitazoxanide	ARG553 ARG555 ASN691 SER759	ASP350 ASP382	SER144 CYS145
Hydroxychloroquine	ARG553	ASN394	ASP187
Anti-inflammatory drugs			

Budesonide	ARG553	ASP350 ASP382	THR26 HIS41
Dexamethasone	ARG553 THR680	ASP350 ASP382	GLU166 LEU141
Methylprednisolone	LYS621 ASN691 SER759	ASP350 ALA348	GLY143 SER144 HIS163
Prednisone	ARG555	ASP350 ALA348	ASN142 LEU141
Hydrocortisone	ARG555 ASN691 SER759 ASP760	ASP350 ASP382 HIS401	GLY143 LEU141 SER144
Prednisolone	ARG555 THR680	ASP382 ASP350	
Parkinson's Disease Drugs			
Amantadine	ASN691	No H-bonds	NO H-BONDS
Levodopa	ARG555 SER682 ASP760	ASN394 ASP350	LEU141 HIS164
Entacapone	ARG555 THR680 ASN691	ALA348 ASP382	SER144 LEU141
Tolcapone	ARG553 ARG555 ARG624 THR680 THR556	ASP382 ASP350 ALA348	SER144 CYS145 LEU141
Bromocriptine	LYS621	ASN394 ASP350	GLU166 ASN142 SER144
Ropinirole	ARG553 THR556 ASP452	ASP350 TYR385	MET165 ARG188

Pramiprexole	SER759 ASP760	ASP350 ASP382 ALA348	GLY143 HIS41
Rotigotine	ARG555 ARG553	SER43	LEU141
Selegiline	No H-bonds	No H-bonds	NO H-BONDS
Rasagiline	SER759 ASP760	PHE390 ARG393	HIS164
Anti-Depressants			
Fluvoxamine	ASP760 SER682 ARG624 TYR456	TYR385 ASN394 ASP382	HIS41 GLY143 LEU141
Fluoxetine	THR556 ALA558 ARG624 ASP623	ASP382 TYR385	SER144
Anti-Coagulants			
Apixaban	ARG553 ARG555	SER47 ASP350	GLU166 CYS145
Edoxaban	ARG555 ASP623	ASP350	GLY143 GLU166 GLN189
Rivaroxaban	ARG555 CYS622 ASP623 SER759	LYS74 ASN394	THR26 CYS145 SER144 GLU166 HIS164
Dabigatran	ARG553 THR556 ASP623	ASN394 GLY395 ASP206 ALA348	ARG188 GLY143 GLU166
Betrixaban	ARG553 ARG555	ASP350 PHE40	GLY143 CYS145

	ASP623	SER44	HIS164
Discontinued Drugs			
Vidarabine	ARG555 ASN691 SER759 SER682	ALA348 TYR385	CYS145 LEU141
Zalcitabine	ARG555 ASP760	ASN394 ASP350	SER144 CYS145 GLU166
Amprenavir	ARG555 ASN691	ASP350 TYR385 SER43	GLY143 CYS145 HIS164 THR24 THR25
Boceprevir	ARG555 ASN691 ASP623 SER759	ASN394 ALA348	THR26
Telaprevir	ARG555 LYS621 ASN691	ASN394 ALA348 ASP350	GLY143 GLU166 HIS163

Table 2: H-bonds of 57 ligands with 7BV2, 6M0J, and 6LU7

4. DISCUSSION

We repurposed commonly available drugs among various categories such as antiviral, anticancer, anticoagulants, anti-inflammatory, Parkinson's disease drugs, antidepressants and discontinued drugs to aid in the fight against COVID-19. We chose three target proteins: Main Protease(PDB ID:6LU7), Spike Glycoprotein (PDB ID: 6M0J), and RNA-dependent RNA polymerase (PDB ID:7BV2) to facilitate our work. We also chose Remdesivir as our reference drug since it is a popular and widely used drug to treat the disease and docked it against our three targets RdRp, Spike and Mpro initially with binding affinities -7.4 kcal/mol, -7.5 kcal/mol and -8.1 kcal/mol respectively. Through our research, we identified 15 drugs in total which either showed comparable or greater affinity to all of our chosen target proteins as compared with Remdesivir. For the target 7BV2, Etoposide exhibited highest binding affinity at -8.4 kcal/mol and formed the H-bonds

ARG555 and ASN691. The target 6M0J bound well to Elbasvir at -11.6 kcal/mol and made the hydrogen bonds with residues TRP69, ASP350, HIS374, and SER409 while Mpro displayed the highest affinity with Vilazodone at -8.8 kcal/mol with H-bonds SER46, THR25 and THR45.While Elbasvir and Bromocriptine showed comparable affinities with 6M0J and 6LU7, they did not dock well with 7BV2. Vilazodone showed higher affinity than Remdesivir with all three targets- RdRp, Spike, and Mpro at -7.6 kcal/mol, -10.0 kcal/mol, and -8.8 kcal/mol respectively. Antiviral drugs Lopinavir (7BV2:6M0J:6LU7::-7.6 kcal/mol, -9.2 kcal/mol, -7.9 kcal/mol), Ritonavir (-7.1 kcal/mol, -8.4 kcal/mol, -7.5 kcal/mol), and Darunavir (-7.9 kcal/mol, -7.9 kcal/mol, -7.9 kcal/mol) showed comparable affinity with our reference drug while anti-parasitic and Parkinson's disease drugs showed least affinity with all three of our target proteins. Anticancer drugs Selinexor (-8.0 kcal/mol, -9.2 kcal/mol, -8.4 kcal/mol), Etoposide (-8.4 kcal/mol, -7.9 kcal/mol, -8.4 kcal/mol), Nintedanib (-7.4 kcal/mol, -8.5 kcal/mol, -7.8 kcal/mol), and anticoagulant drugs , Rivaroxaban (-7.7 kcal/mol, -7.9 kcal/mol, -7.8 kcal/mol), Dabigatran (-8.2 kcal/mol, -8.6 kcal/mol, -7.5 kcal/mol), and Betrixaban (-8.0 kcal/mol, -7.9 kcal/mol, -8.3 kcal/mol) also showed promising results with the three target proteins. Two anti-inflammatory drugs Methylprednisolone (-7.1 kcal/mol, -7.9 kcal/mol, -8.0 kcal/mol) and Hydrocortisone (-6.9 kcal/mol, -7.4 kcal/mol, -8.1 kcal/mol), one Parkinson's disease drug Tolcapone (-7.2 kcal/mol, -7.1 kcal/mol, -7.6 kcal/mol), one discontinued drug Amprenavir (-7.2 kcal/mol, -8.1 kcal/mol, -7.7 kcal/mol) also proved comparable with Remdesivir. The ligands bound well to 6M0J- spike glycoprotein. In general, anticancer and anticoagulant drugs bound well to all of the three target proteins.

5.   ADME PREDICTION

The prediction of various physiochemical and pharmacokinetic properties was done using SwissADME (http://www.swissadme.ch/index.php). Ritonavir and Etoposide do not satisfy the Lipinski rule of 5 due to Molecular weight and NorO violations, which exceeded the acceptable range. Vilazodone, Methylprednisolone, Hydrocortisone, Tolcapone, Apixaban, Rivaroxaban, Dabigatran and Betrixaban satisfied all of Lipinski's rules and are deemed orally active. Lopinavir, Darunavir, Selinexor, Nintedanib, and Amprenavir also satisfy Lipinski's rules with one violation of high molecular weight, making them orally active. Table 3 shows the Lipnski's rules for the shortlisted drugs.

Drug	Mass (<500 Dalton) g/mol	Hydrogen Bond Acceptors(< 10)	Hydrogen Bond Donors(<5)	MLOGP(<5)	Lipinski rule violations
Vilazodone	441.52	4	2	1.6	Yes- 0
Lopinavir	632.83	5	4	2.93	Yes-1
Ritonavir	724.98	7	4	1.8	No-2
Darunavir	549.68	8	3	1.18	Yes-1
Selinexor	443.31	11	2	1.18	Yes-1
Etoposide	588.56	13	3	-0.14	No-2
Nintedanib	541.64	7	2	2.36	Yes-1
Methylprednisolone	375.48	5	3	1.52	Yes-0
Hydrocortisone	363.47	5	3	1.39	Yes-0
Tolcapone	274.25	5	3	0.97	Yes-0
Apixaban	459.50	5	1	2.03	Yes-0
Rivaroxaban	435.88	5	1	1.41	Yes-0
Dabigatran	476.55	6	4	1.63	Yes-0
Betrixaban	453.92	5	3	2.56	Yes-0
Amprenavir	509.66	7	3	1.14	Yes-1

Table 3: **Lipinski rules for shortlisted drugs from SwissADME**

Cytochrome inhibitors

The cytochromes belonging to the P450 subfamily are enzymes responsible for a host of metabolic activities. One key cytochrome is the CYP3A4 which is responsible for oxidation of small molecules leading to their excretion from the body. Lopinavir, Ritonavir, Darunavir, Selinexor, and Amprenavir inhibit this cytochrome but do not inhibit the rest from the same subfamily suggesting low gastrointestinal absorption [23]. Table 4 showcases the cytochrome inhibitors for chosen drugs.

Drug	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Vilazodone	no	yes	yes	yes	yes
Lopinavir	no	no	no	no	yes

Ritonavir	no	no	no	no	yes
Darunavir	no	no	no	no	yes
Selinexor	no	no	no	no	yes
Etoposide	no	no	no	yes	no
Nintedanib	no	yes	yes	yes	no
Methylprednisolone	no	no	no	no	no
Hydrocortisone	no	no	no	no	no
Tolcapone	no	no	no	no	no
Apixaban	no	yes	yes	yes	yes
Rivaroxaban	no	yes	yes	no	yes
Dabigatran	no	yes	no	no	no
Betrixaban	no	yes	no	no	no
Amprenavir	no	no	no	no	yes

Table 4: **Cytochrome Inhibitors for shortlisted drugs from SwissADME**

Bioavailability

Oral bioavailability of a drug depends on six properties as predicted by SwissADME. The lipophilicity of a drug as determined by XLOGP3 should be in the range −0.7 and +5.0, the size as determined by the mass should be in between 150 and 500 g/mol, the polarity as determined by TPSA should exist between 20 and 130 Å^2, the solubility as determined by Log S (ESOL) should not be greater than 6, saturation as determined by fraction csp3 must be greater than 0.25, and finally, the flexibility as determined by the number of rotatable bonds must not exceed 9.

Taking these properties into consideration, the drugs available orally are Vilazodone. Methylprednisolone, Hydrocortisone, Apixaban, and Rivaroxaban. Out of these, Vilazodone are moderately soluble while Methylprednisolone, Hydrocortisone and Rivaroxaban are soluble. Table 5 showcases the bioavailability factors of the shortlisted drugs.

Drug	Lipophilicity XLOGP3	Mass (<500 Dalton) g/mol	TPSA	Log S (ESOL)	ESOL Class	Fraction csp3	Rotatable bonds
Vilazodone	3.98	444.55	102.29	-5.05	Moderately soluble	0.31	7

Lopinavir	5.92	632.83	120	-6.66	Poorly soluble	0.43	17
Ritonavir	6.05	724.98	202.26	-7.02	Poorly soluble	0.43	22
Darunavir	2.94	549.68	148.8	-4.48	Moderately soluble	0.52	13
Selinexor	2.94	445.32	97.62	-4.48	Moderately soluble	0.12	8
Etoposide	0.6	588.56	160.83	-3.75	Soluble	0.55	5
Nintedanib	4.3	541.64	101.47	-5.7	Moderately soluble	0.26	9
Methylprednisolone	1.95	375.48	94.83	-3.26	Soluble	0.73	2
Hydrocotisone	1.61	363.47	94.83	-2.98	Soluble	0.81	2
Tolcapone	2.83	274.25	107.19	-3.57	Soluble	0.07	3
Apixaban	2.24	459.5	110.76	-4.14	Moderately soluble	0.28	5
Rivaroxaban	2.49	435.88	116.42	-4	Soluble	0.32	6
Dabigatran	1.7	476.55	150.22	-3.65	Soluble	0.16	10
Betrixaban	3.56	453.92	107.41	-4.72	Moderately soluble	0.13	9
Amprenavir	2.89	509.66	139.57	-4.22	Moderately soluble	0.48	13

Table 5: Bioavailability factors for shortlisted drugs from SwissADME

6. CONCLUSION

Vaccines are a preventative form of medicine. While effective in decreasing the effect caused due to the exposure of the disease, it cannot help people who are already suffering. At this stage, we are going through the second wave of the COVID-19 pandemic with three FDA-approved vaccines for emergency use- Pfizer-BioNTech vaccine, Moderna Vaccine, Janssen vaccine- and one approved repurposed drug- Remdesivir. While most of the world is taking part in vaccination drives and various lockdowns, India and Brazil are currently the most affected countries ravaged by this

disease, with thousands dying every day and a severe lack of vaccines, equipment, drugs, and hospital facilities to deal with the pandemic. Repurposing commonly available and commonly used drugs provides a shortcut to understanding and decreasing the effects of the disease. Since repurposing involves already approved drugs, it cuts short the time required to formulate, assessing the side-effects and undergoing various clinical trials. Since Remdesivir is the only approved drug to treat the disease, its scarcity and price pose a massive hindrance to overcoming this pandemic. Out of the 57 repurposed drugs, we shortlisted fifteen based on the binding affinity and H-bond interactions, which are likely to prove beneficial in fighting the disease. These drugs are: Vilazodone (CNS drug), Lopinavir (Antiviral), Ritonavir (Antiviral), Darunavir (Antiviral), Selinexor (Anticancer), Etoposide (Anticancer), Nintedanib (Anticancer), Methylprednisolone (anti-inflammatory), Hydrocortisone (anti-inflammatory), Tolcapone (Parkinson's disease drug), Apixaban (anticoagulant), Rivaroxaban (anticoagulant), Dabigatran (anticoagulant), Betrixaban (anticoagulant), and Amprenavir (discontinued drug). We recommend these drugs for further in vitro and in vivo studies to determine their efficacy in fighting the disease.

7.   ACKNOWLEDGMENTS

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