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ANTI HEPATITIS C VIRAL DRUGS REMDESIVIR AND UPRIFOSBUVIR DERIVATIVES ARE BETTER INHIBITORS OF SARS COV2 RNA-DEPENDENT RNA POLYMERASE DETERMINED BY DOCKING.

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Abstract: SARS Cov2 RNA-dependent RNA polymerase (RdRp) is an enzyme that catalyzes the synthesis and replication of viral RNA from an RNA template. Our starting model for this study was (SARS-Cov-2) cryo-EM structure published recently (PDB ID 6M71). We have used docking studies to find a better inhibitor for the enzyme that can be used in the treatment of SARS-CoV2 infections. Recently, several inhibitors like Sofosbuvir, Ribavirin, and Remdesivir has been reported as strong inhibitors of this enzyme. Our results show an analogue of Remdesivir such as CHEMBL3120791 and analogue of Uprifosbuvir SCHEMBL20762917, SCHEMBL20733228 as better inhibitors than previously reported inhibitors of RNA-dependent RNA polymerase. Using Autodock Vina and Pyrx software for virtual screening of ligands, we found four higher efficiency compounds CHEMBL3120791, SCHEMBL20762917, SCHEMBL20733228 and Uprifosbuvir. The binding constant of these ligands were -9.5 (Kcal/mol), -8.3 (Kcal/mol), -8.3 (Kcal/mol), -8.6 (Kcal/mol), respectively when tested on SARS-COV-2 nsp12. Active site interactions with the potential drug molecule are with residues Lys47, Tyr129, Ser784, His133 and Ser709 for CHEMBL3120791, SCHEMBL20762917 and SCHEMBL20733228. These molecules can be used in the future drug development process in the treatment of SARS-Cov2 infection. The molecules reported here are already under clinical trial for the treatment of HCV (Hepatitis C Virus) infections, which is similar to SARS Cov2, as both are positive-sense RNA Viruses. We also investigated binding efficacy of these identified inhibitors against SARS spike protein for this, we used pdb files 2GHV (SARS spike protein receptor binding domain) and 5XLR (SARS CoV spike glycoprotein). In addition, 1P9U which is coronavirus main proteinase was also evaluated. The compounds identified and reported here also showed better binding affinity towards these proteins.

Keywords: SARS Cov2, RNA-dependent RNA polymerase, RdRP, Docking, Drug Design, Hepatitis C Virus, Remdesivir, Uprifosbuvir, CHEMBL3120791, SCHEMBL20762917 SCHEMBL20733228, 6M71, 2GHV, 5XLR, 1P9U

I. INTRODUCTION

SARS CoV-2 virus that causes COVID-19 respiratory disease has emerged as one of the deadly pathogens of the 21st century [1]. SARS CoV2 is an enveloped non segmented positive sense RNA coronavirus belonging to genus Betacoronavirus [2]. This genus also includes two other RNA viruses that has caused epidemics like Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV and Middle East Respiratory Syndrome (MERS) caused by MERS-CoV [3], [4]. Due to high affinity of the viral spike protein with host receptor, infection of SARS CoV-2 is known to increase exponentially thereby increasing human to human transmission [5].

RNA dependent RNA polymerase (RdRp) of SARS COV-2 is known to mediate replication of the viral genome and its propagation inside host cells [6]. The core component of RdRP is nsp12 (nonstructural protein) which has little activity but together with nsp7 and nsp8 can increase RdRP template binding and processivity rate [7], [8] RdRP is also the target of a class of antivirals like Remdesivir [9] that has come into spotlight recently as human clinical trials have shown promise in treatment of COVID-19. Remdesivir is a nucleotide analog and is a prodrug that is converted to active drug in triphosphate form inside cells [10], [11].

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Angiotensin converting enzyme (ACE2) receptor has been identified as the entry point for SARS virus into host cells [12]. ACE2 is expressed in various organs and tissues namely lungs, cardiovascular system, gut, kidneys, central nervous system, and adipose tissue [13]. The spike protein of SARS virus has strong binding affinity for the ACE2 receptor. Although SARS CoV-2 receptor binding domain has close homology to most SARS virus, there are several amino acids that are different [14]. These differences in amino acid composition allow SARS CoV2 to bind to ACE2 with higher affinity thereby spreading the disease and enabling viral replication [15].

Apart from ACE2 receptor and SARS CoV2 RdRp, coronavirus main proteinase (3CL ^{pro}) has also been reported as a potential drug target against SARS virus [16 - 18]. This proteinase is a major component of coronavirus replication complex and belongs to the cysteine protease family, it also plays a major role in processing polyproteins [19]. Inhibition of this proteinase function will hamper replication and proliferation of the virus [20].

In this report we have used docking studies with Remdesivir as well as its analogues and Ribavirin, Uprifosbuvir, Adafosbuvir and several other compounds to find the best inhibitor for RdRp. We identified a few compounds that had better efficacy not only towards RdRp but also can be used for inhibition of SARS main proteinase 3CLpro and SARS CoV2 spike glycoprotein. Thus the inhibitors identified in this docking study can be used as a broad spectrum inhibitor for number of target proteins present in SARS CoV2. We believe these results will enable us to design better drugs for the treatment of this deadly virus.

II. Material & Methods

A. Protein

Protein File: In this study, the structure of SARS CoV-2 RdRP (RNA-dependent RNA polymerase) was used as a starting model (PDB ID 6M71) [21 - 22]. The structure was obtained from the RCSB website with pdb ID 6M71. This is a 2.9Å resolution cryo EM structure consisting of 4 chains, which are A, B, C and D. In this structure A Chain is the SARS-Cov2 nsp12, B, D chains are SARS-Cov2 nsp8 and C Chain is SARS-COV-2 nsp7. Recent reports by Kirchdoerfer, R.N., Ward et.al indicates that all three non-structured proteins are assembled to form the RdRp enzyme [23].

B. Chemical Data

Chemical Data: The data for the inhibitors were collected from Pubchem [24] which includes various antiviral drugs such as Ribavirin, Uprifosbuvir, Remdesivir, Adafosbuvir, and their analogs. Remdesivir is a potential inhibitor for SARS-Cov-2 RNA-dependent RNA polymerase. Remdesivir interacts with active site residues Arg-555, Ser-549 and Asp-618 of this RdRP protein [17]. Ribavirin is a synthetic nucleoside analog of ribofuranose with activity against hepatitis C virus and other RNA viruses [25 - 26], Uprifosbuvir is under investigation in clinical trial for Hepatitis C Virus (HCV) [27], Adafosbuvir also exhibits antiviral activity [28]. In order to find a better inhibitor that binds RdRp with better binding efficiency than Remdesivir, we selected thirty one compounds in our docking studies.

Table 1: Thirty one compounds used for this docking studies

S.No	Pubchem ID	Chemical Name
1	CID5064 [39]	ICN 1229
2	CID37542 [40]	Ribavirin
3	CID100252 [41]	Ribavirin monophosphate
4	CID122108 [42]	Ribavirin 5'-triphosphate
5	CID124970 [43]	Ribavirin 5'-diphosphate
6	CID129235 [44]	Ribavirin 5'-sulfamate
7	CID362949 [45]	SCHEMBL6981526
8	CID451448 [46]	Ribavirin amidine
9	CID451949 [47]	dd-ribavarin
10	CID452722 [48]	3'-Deoxyribavirin
11	CID460516 [49]	Levovirin, L-Ribavirin
12	CID6713992 [50]	Ribavirin E
13	CID10220469 [51]	SCHEMBL1981630
14	CID11436477 [52]	alpha-Ribavirin
15	CID40629571 [53]	SCHEMBL326516
16	CID54759694 [54]	CHEMBL3120793
17	CID70989848 [55]	SCHEMBL13761348
18	CID76325303 [56]	CHEMBL3120791
19	CID90055716 [57]	Uprifosbuvir
20	CID118596336 [58]	Adafosbuvir
21	CID121304016 [59]	Remdesivir
22	CID137465280 [60]	SCHEMBL20705434
23	CID137490591 [61]	SCHEMBL20733226
24	CID137490593 [62]	SCHEMBL20733228
25	CID137509756 [63]	SCHEMBL20754604
26	CID137517260 [64]	SCHEMBL20762917
27	CID137517361 [65]	SCHEMBL20763026
28	CID45375808 [66]	Sofosbuvir
29	CID6440764 [67]	Thymectacin
30	CID3652 [68]	Hydroxychloroquine
31	CID71826 [69]	Cletoquine

Table 1 shows Ribavirin, Uprifosbuvir, Adafosbuvir, Remdesivir, Sofosbuvir, Themetacin, Hydroxychloroquine, and related analogues of these molecules. These molecules were docked against protein structure 6M71 using PyRx and Autodock Vina.

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C. Docking Studies

We performed docking studies using two different strategies, first we excluded B, C and D chains and used only "A" chain for docking and in the second iteration we used all 4 chains which is the complete enzyme complex. Recent reports indicate that nsp12(chain A) has low template binding and processivity rate by itself, for efficient binding and activity the whole enzyme complex with chain A, B, C & D are required [7 - 8]. Hence, we also performed docking studies with the whole enzyme complex comprising of nsp12, nsp7 and nsp8. For Docking, we used Autodock [29], Autodock Vina [30] and PyRx [31]. Apart from selective ligands, we have used control, which are Sugar [70], Maltose [71], and Amino Sugar [72].

In order to investigate whether these inhibitors can also work with spike protein inhibition of SARS-CoV2 we downloaded pdb file for spike protein of SARS-CoV2. The pdb file used for this was 2GHV [32], which is receptor binding domain of SARS spike protein. We also performed docking studies using 5XLR (SARS-CoV2 spike glycoprotein) [33], 1P9U (Corona virus main proteinase 3CLpro) [20].

III. Results and Discussion

In this report we have performed docking studies with 31 different molecules that are Remdesivir analogues (Table 1). We have used Autodock, Autodock Vina, and PyRx virtual screening software. Our starting pdb was 6M71 which is RNA dependent RNA polymerase of SARS CoV-2.

Out of 31 compounds used for our docking studies we identified four compounds that produced better binding efficiency than Remdesivir particularly with chain A or nsp12 molecule alone. These compounds are CHEMBL3120791, SCHEMBL20733228,Uprifosbuvir and SCHEMBL20762917.

Our Rational behind using CHEMBL3120791 and SCHEMBL20733228 originates from the fact that these two compounds has been reported to exhibit antiviral activity against HCV (Hepatitis C Virus) genotype 1b [34]. In this study, human HuH7 cells were used and when treated with these compounds the viral replication was inhibited after 3 days studied by luminescence assay. Previous studies have shown SCHEMBL20733228 and Uprifosbuvir exhibited antiviral activity against HCV infections [27], [35]. Most of these drugs are under clinical trials.

In our docking studies with chain A (SARS-COV-2 nsp12) better binding affinity was observed with four compounds identified as CHEMBL3120791, SCHEMBL20733228, Uprifosbuvir and SCHEMBL20762917. The respective binding energy for these compounds were: CHEMBL3120791 -9.5 Kcal/mol, SCHEMBL20733228 : -8.3 Kcal/mol, Uprifosbuvir -8.6 Kcal/mol and SCHEMBL20762917 with -8.3 Kcal/mol. Remdesivir in comparison had much lower binding energy of -6.8 kcal/mol (Table 2)

Table 2: Binding Energy of ligands on "A" Chain SARS-COV-2 nsp12 Only. Controls: Sugar -6.8, Maltose -6.8 and Amino sugar with -5.6 Kcal/mol.

Ligand (Pubchem Id)	Binding Energy (Kcal/mol)	Chemical Name
CID76325303	-9.5	CHEMBL3120791
CID137490593	-8.3	SCHEMBL20733228
CID90055716	-8.6	Uprifosbuvir
CID137517260	-8.3	SCHEMBL20762917
CID 45375808	-8.0	Sofosbuvir
CID137509756	-8.3	SCHEMBL20754604
CID137517361	-8.8	SCHEMBL20763026
CID121304016	-6.8	Remdesivir

Table 3: Binding Energy of ligands on All Chains, which Includes nsp12, nsp8, nsp7. Controls: Sugar -6.8, Maltose -6.3 and Amino sugar with -5.4 Kcal/mol

Ligand (Pubchem Id)	Binding Energy (Kcal/mol)	Chemical Name
CID90055716	-8.8	Uprifosbuvir
CID76325303	-8.5	CHEMBL3120791
CID137517260	-8.3	SCHEMBL20762917
CID121304016	-8.2	Remdesivir
CID45375808	-7.8	Sofosbuvir
CID137490591	-7.7	SCHEMBL20733226
CID137490593	-7.7	SCHEMBL20733228
CID137509756	-7.7	SCHEMBL20754604
CID118596336	-7.6	Adafosbuvir

Docking results with all four chains which include nsp12, nsp7 and nsp8, yielded the following binding energies: Uprifosbuvir: -8.8 Kcal/mol, CHEMBL3120791: -8.5 Kcal/moll, SCHEMBL20762917: -8.3 Kcal/mol. The binding energy with Remdesivir is -8.2 kcal/mol, which is close to the compound studied here. (Table 3)

From our docking studies, with the better binding energy compounds, active residues identified were Lys47, Ser784, Ser709, Tyr129, His133, Thr141 using Ligplus+ (Fig. 1) (Table 4)

Fig. 1. CHEMBL3120791 (CID76325303) with 6M71 using LigPlus+ (unk0 = CID76325303)

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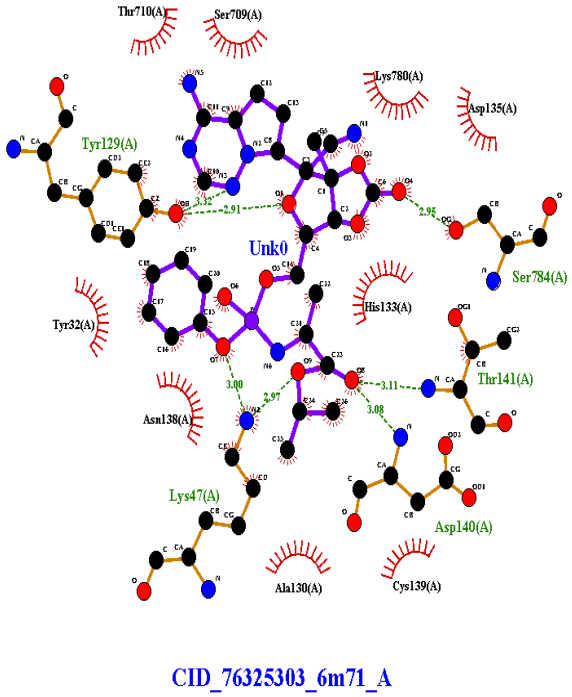


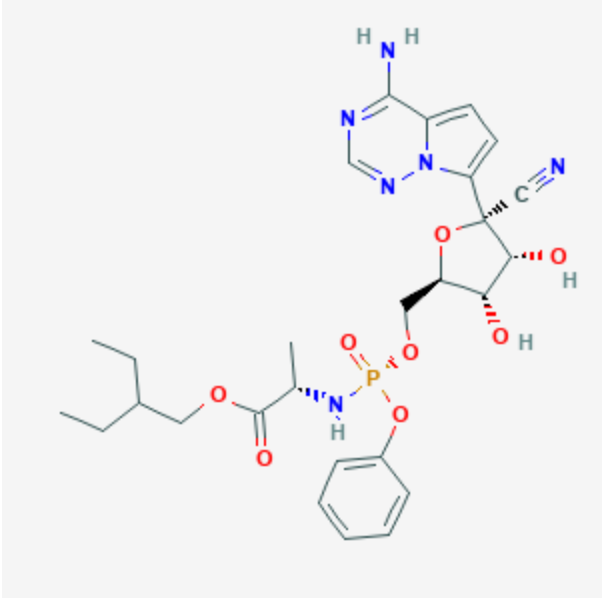
Table 4: Using LigPlus+, the active site amino acids for these Ligand Molecule on Chain A –nsp12

S.No	Ligands	Active Site Amino Acids
1	CHEMBL3120791 (CID76325303)	Lys47, Ser784, Tyr129, His133
2	SCHEMBL20733228 (CID137490593)	Lys 47, Ser709, Thr141, His133
3	SCHEMBL20762917 (CID137517260)	Lys47, Ser784, Tyr129, His133, Ser709, Asn781
4	CID90055716 (Uprifosbuvir)	Lys47, His133, Tyr129, Ser709, Thr141

CHEMBL3120791 is Remdesivir analogue, where as SCHEMBL20733228, and SCHEMBL20762917 are Uprifosbuvir analogue. They are potential inhibitors, and have previously shown antiviral activity in wet lab analysis in case of HCV virus [27]. We believe efficacy of these potential inhibitors can be tested against SARS Coronavirus 2 – RdRP. The conformational stability of this molecule can be tested using Molecular Dynamic simulation. Further experimental data in wet-lab will provide evidence of the efficacy of these molecules. Structural difference are shown in Fig. 2 and Fig. 3

Fig. 2. Structural difference of high binding energy molecules with Remdesivir and CHEMBL3120791.

2. (a) Remdesivir (CID121304016)



2. (b) CHEMBL3120791

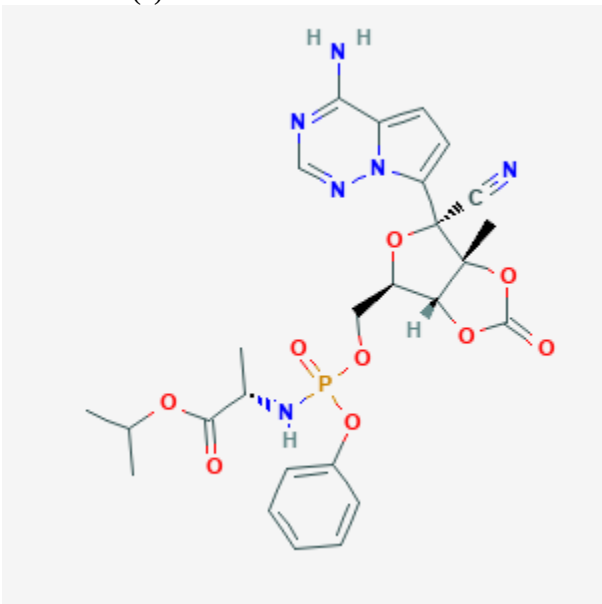


Fig 3. Structural differences with Uprofosbuvir, SCHEMBL20762917 and SCHEMBL20733228.

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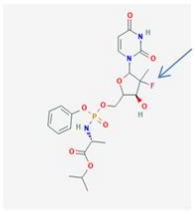
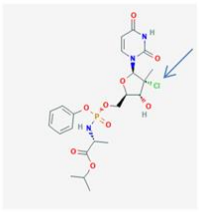
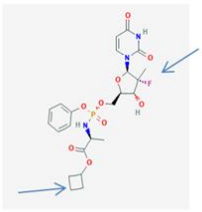

SCHEMBL20733228
(CID_137490593)


Uprifosbuvir
(CID_90055716)


SCHEMBL20762917
(CID_137517260)

The hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus which is similar to Coronaviruses which have positive-sense, single-stranded RNA genome [38]. The inhibitor identified in this study has been tested against HCV virus [27].

We also investigated binding efficacy of these identified inhibitors against SARS spike protein for this we used pdb files 2GHV (SARS spike protein receptor binding domain) and 5XLR (SARS CoV spike glycoprotein). In addition, 1P9U which is coronavirus main proteinase was also evaluated. The compounds identified and reported here also showed better binding affinity towards these proteins. (Table 5)

Table 5: Binding Energy with other than RNA dependent RNA polymerase: PDB Id's 2GHV, 5XLR, 1P9U. Binding Energy in (Kcal/mol).

S.No	Ligand	2GHV	5XLR	1P9U
1	CHEMBL3120791	-7.4	-8.8	-9.5
2	SCHEMBL20733228	-6.4	-8.5	-8.5
3	SCHEMBL20762917	-7.0	-8.2	-8.8
5	Uprifosbuvir	-6.9	-7.8	-8.5
5	Remdesivir	-6.5	-2.8	-9.3

IV. CONCLUSION

From these studies we can conclude that analogue of Remdesivir such as CHEMBL3120791 and analogue of Uprifosbuvir such as SCHEMBL20762917, SCHEMBL20733228 can be potentially used not only in the prevention of viral RNA replication but also against virus receptor binding reaction. If the spike protein is inhibited from binding human ACE2 receptor viral load can be decreased. The main proteinase of SARS virus also was inhibited with these compounds. The inhibitors identified here can be tested further in human clinical trials as they exhibit better binding than Remdesivir and Uprifosbuvir.

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