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# Docking Results and in Silico Studies Indicating Beta-lapachone can be a Potent SARS-CoV-2 Inhibitor for Therapeutic Investigations & Future International Clinical Trials

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**ABSTRACT:** Outbreak and pandemic of coronavirus SARS-CoV-2 in 2019-20 giving continuous threat to global health and because of selected categories of drugs are under an experimental stages and also not achieved a satisfactory level of effective result then we herein try to find out a potent and effective inhibitor. Blockade of ACE2 the host cell receptor for the S protein of SARS-CoV-2 and inhibition of TMPRSS2, which is required for S protein priming may prevent cell entry of SARS-CoV-2 and inhibit infection and replication of SARS-CoV-2. There is also potential for targeting other highly conserved proteins associated with SARS-CoV and SARS-CoV-2, including RdRp is an RNA-dependent RNA polymerase required for replicating the viral genome within the host cell. RdRp is directly mediates the replication and transcription of RNA from RNA strand. Transcription of type 1 human Immunodeficiency virus (HIV-1) provirus is governed by the viral long terminal repeat (LTR). Drugs can block HIV-1 replication by inhibiting activity of its LTR. Beta-lapachone is potent and selective inhibitor of HIV-1 LTR-directed gene expression, at concentrations that have minor effects on cells. Our focus on a comparative docking analysis of antiviral drugs, such as the remdesivir, active form of remdesivir, broad-spectrum antiviral drugs favipiravir and beta lapachone and try to find out the reasons of anti covid-19 potency for beta-lapachone which may resist spread of SARS-CoV-2 and morbidity and mortality of COVID-19 pandemic when others drugs showing non satisfactory results. Drug repositioning may offer a strategy and a number of drugs have been repurposed, including lopinavir, remdesivir, favipiravir and therefore **beta-lapachone** may demand as a future potent candidate drug for covid-19 and specially beta lapachone need an international clinical trials for covid-19.

**KEYWORDS:** SARS-CoV-2, RdRp, HIV-1 LTR, Beta-lapachone, Remdesivir, Docking, Vina, Desmond

## I. INTRODUCTION

The outbreak and global threat of coronavirus SARS-CoV-2 in Wuhan, China in December 2019, has spread more than 185 countries forced to WHO to declare COVID-19 as a pandemic on March 11th 2020 [1]. Millions of lives have been affected as a result of mandatory quarantines. Corona viruses are grouped into alpha, beta, gamma, and delta classes, can infect both humans and animals.  $\gamma$ - and  $\delta$ -coronaviruses are more inclined to infect birds, while  $\alpha$ - and  $\beta$ -coronaviruses mainly infect mammals [2]. A phylogenetic analysis has demonstrated that the new coronavirus significantly clustered with the sequence of bat SARS-like coronavirus [3]. It has envelopes, and the particles are round or oval with diameter from 60 to 140 nm [4]. As for other coronaviruses, the replication of SARS-CoV-2 starts with the attachment to the host cell through interactions between Spike protein (S protein) and its target protein. Coronavirus SARS-CoV-2 is believed to be bats, which carry the virus with no signs of disease [5]. Beta coronaviruses caused earlier outbreaks of severe acute respiratory syndromes (SARS), including SARS-CoV (Guangdong, China in 2002/2003) and Middle East Respiratory Syndrome virus MERS-CoV (Saudi Arabia in 2012) [6]. Beta coronaviruses have a single stranded RNA genome, whose genome encodes are structural proteins, non-structural proteins and accessory proteins [7]. The coronavirus crown-like ("corona") morphology is created by transmembrane spike glycoproteins (S proteins) that form homotrimers protruding from the viral surface [8]. The S proteins of SARS-CoV and SARS-CoV-2 display structural homology and conserved ectodomains, since SARS-CoV-2 also employs ACE2

for cell entry [9,10]. Similar to the earlier SARS and MERS beta coronaviruses, SARS-CoV-2 primarily infects alveolar epithelial cell of the lung, leading to a severe bilateral peripheral pneumonia with ground glass opacity in CT images (COVID-19 disease), with a mortality rate of 2 % to 5 % [11] & can contribute to multiple organ failure, affecting heart, liver, kidney, central nervous system and gastrointestinal tract [12]. After host cell entry, the viral single-stranded positive RNA is released for replication of virus RNA and translation of virus polyproteins that are finally cleaved into mature effector proteins by virus proteases [13]. Strategies capable of disrupting S protein interaction with ACE2 could be of significant therapeutic value. There is also potential for targeting other highly conserved proteins associated with SARS-CoV and SARS-CoV-2, including RdRp (nsp12, 95% similarity between two virus) is an RNA-dependent RNA polymerase required for replicating the viral genome within the host cell. 3C<sub>pro</sub> (nsp5, 96% similarity) and P<sub>pro</sub> (nsp3, 83% similarity) are both viral proteases which break down viral polyprotein into functional units within host cells that are finally assembled into new viruses. Drugs that have recently been shown to target MERS-CoV in mice [14], and to inhibit Ebola virus RdRp and SARS-CoV-2 proteases in humans, such as remdesivir and ritonavir/lopinavir, also constitute candidate drugs against SARS-CoV-2 and are now investigated for their therapeutic efficacy in COVID-19 patients in 2 international clinical trials (SOLIDARITY Trial and DisCoVeRy Trial). Finally, certain phytochemicals and natural products with high antiviral activity like **beta lapachone, nicotiana, flavipiravir** should be considered for treatment of SARS-CoV-2 infection and COVID-19 disease. Here mainly we have compared the positions, scoring values, interacted residues between RdRp of SARS-CoV-2 and different ligands after docking and assuming that beta-lapachone would be a future potent anti covid-19 agent.

## II. INHIBITORS OF REPLICATION AND ASSEMBLY OF SARS-CoV-2

**1. Remdesivir** : Remdesivir is a novel small-molecule adenine nucleotide analogue antiviral drug that has shown efficacy against Ebola virus in rhesus monkeys. Remdesivir is a prodrug that is metabolized into its active form GS-441524, an adenine nucleotide analogue that interferes with the activity of viral RNA-dependent RNA polymerase (RdRp) and that promotes evasion of proof reading by viral exoribonuclease, leading to inhibition of viral RNA synthesis [15]. Remdesivir acts early in infection, and decreases viral RNA levels in a dose-dependent manner that parallels impairment of viral load in vitro [15]. These and related mechanisms of action of remdesivir have been demonstrated in vitro for SARS-CoV [15], Ebola virus [16] and MERS-CoV [17]. A recent study demonstrates in cell culture experiments with simian Vero E6 cells infected with SARS-CoV-2 that remdesivir is inhibitive against SARS-CoV-2 infection at EC 90 of 1.76  $\mu$ M, a concentration achieved in vivo in nonhuman primate models [36]. It was further shown that remdesivir efficiently inhibited SARS-CoV-2 infection of human liver cancer Huh-7 cells, which are sensitive to SARS-CoV-2 infection [18]. A recent clinical trial with remdesivir for a compassionate use to 53 COVID-19 patients receiving oxygen support or mechanical ventilation due to an oxygen saturation of 94 % or less demonstrated that intravenous treatment with 200 mg remdesivir at day 1, followed by 100 mg daily for 9 days, resulted in clinical improvement in 36 of the 53 patients (68 %) [83]. However, the mortality rate was 18 % among patients receiving invasive ventilation and 5% among patients not receiving invasive ventilation [19], suggesting that remdesivir constitutes a therapeutic option for COVID-19 patients not receiving invasive ventilation. Remdesivir has been recently recognized as a promising antiviral drug against a broad spectrum of RNA viruses (including MERS-CoV) infection in cultured cells, mice and non-human primate models [20]. Recent results from a preclinical study indicated that, in vitro, the association remdesivir/chloroquine could be highly effective in controlling the SARS-Cov-2 infection. The efficacy and safety of remdesivir are currently being evaluated in a phase 3 clinical trial in 237 patients with COVID-19, which ended on April 10, 2020 [21]. In addition, a further phase 3 trial is evaluating the efficacy and safety of remdesivir in 1,600 patients with COVID-19; this study will end in May 2020 [21].

**2. Favipiravir**: Favipiravir (Avigan<sup>TM</sup>), (T-705), (6-fluoro-3-hydroxy-2-pyr-azinecarboxamide), (CAS number: 259793-96-9), is an oral pyrazinecarboxamide derivative and guanine analogue developed by Toyama Chemical, Japan that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses and induces lethal RNA transversion mutations, thereby producing a nonviable virus phenotype [22-24]. Favipiravir inhibits replication of a large number of RNA viruses, including influenza A virus, flavi-, alpha-, filo-, bunya-, arena- and noroviruses as well as West Nile virus, yellow fever virus, foot-and-mouth-disease virus, Ebola virus and Lassa virus [25-26]. As reported by Watanabe (2020) [27], favipiravir was administered during a clinical trial to 200 patients with COVID-19 at hospitals in Wuhan and Shenzhen. The results of these studies showed that patients who received the drug tested negative in a relatively short time (4 days compared to 11 days in the control group), while the symptoms of pneumonia were significantly reduced. No specific safety concerns have emerged. Another clinical study carried out in Wuhan showed that favipiravir-treated patients recovered from fever after an average of 2.5 days compared to 4.2 days in other patients. Chang Chen et al. (2020) [28] recently published the results of a randomized clinical trial [29], which

compared the efficacy and safety of favipiravir versus umifenovir in the treatment of 240 patients with COVID-19, hospitalized in three hospitals from February 20, 2020, to March 12, 2020. These results showed that the 7-day clinical recovery rate was 55.86% in the umifenovir group and 71.43% in the favipiravir group ( $P = 0.01$ ). patients with hypertension and/or diabetes, the time for fever reduction and cough relief was significantly shorter in favipiravir group than in umifenovir group ( $P < 0.001$ ), but no statistically significant difference regarding oxygen therapy or non-invasive mechanical ventilation was found. The most common adverse events were liver enzyme abnormalities, psychiatric, gastrointestinal symptoms and serum uric acid elevations (2.5% of patients in the umifenovir group vs. 13.79% of patients in the favipiravir group,  $P < 0.0001$ ).

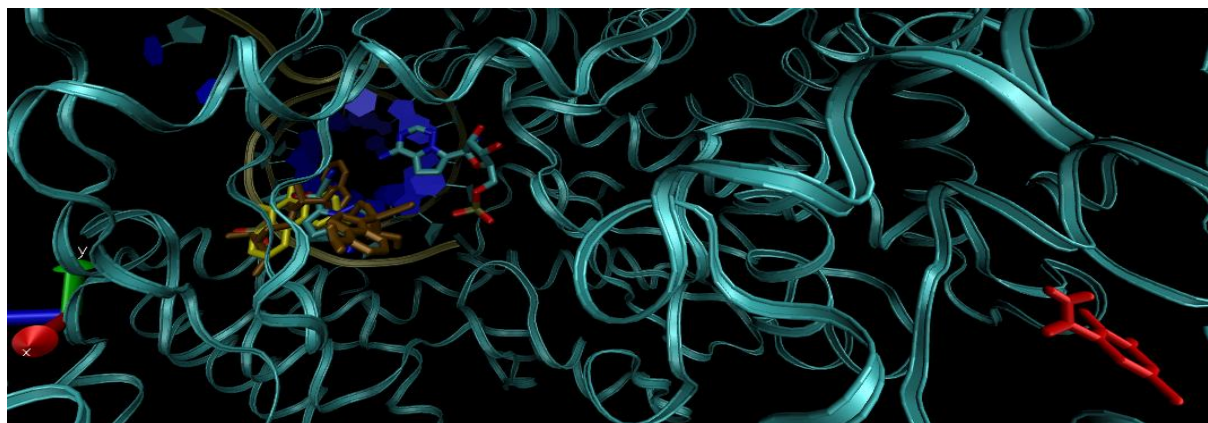
**3. Beta-Lapachone :** The evolution of type 1 human immunodeficiency virus (HIV-1) infection and the progression of immunosuppression are associated with activation of latent provirus, which is governed by long terminal repeat (LTR) in the viral DNA [30-33]. The activity of the HIV-1 LTR is determined by the complex interaction of positive and negative transcriptional regulators that bind to specific sequences within the LTR [30-31]. Changes in the quantity or quality of these factors may underlie the activation of transcription of HIV-1 latent provirus by a myriad of stimuli [32,33]. In particular, phorbol 12-myristate 13-acetate (PMA) and tumor necrosis factor  $\alpha$  (TNF) are potent activators [30-32-34]. TNF may play a critical role in the pathogenesis of AIDS, consistent with markedly increased levels of this cytokine in HIV-1-infected individuals [35]. Compounds that block activation or suppress the activity of HIV-1 LTR are of therapeutic potential for extension of latency or inhibition of persistent progressive infection. beta-Lapachone, which is isolated from plant extracts [36], has a variety of pharmacological effects [37-38]. Toxicity data in humans are not available for (beta-lapachone; it is well tolerated in mice at  $<40$  mg/kg given i.v. (unpublished data). The maximum tolerated dose is about 1250 mg/kg given orally in mouse and chicken [37]. Transcriptional promoter located in the long terminal repeat (LTR) of the HIV-1 genome, which is one of the most conserved regions among virus isolates and subtypes. This relative conservation indicates that the LTR is subject to strict constraints because it is important for viral gene expression and replication. The LTR of HIV-1 can be subdivided into the U3, R, and U5 regions, the first two of which are essential for transcription. Upon transcription, the R region folds the TAR hairpin structure that interacts with the viral Tat protein to fully activate transcription. The U3 region contains the TATA box and several upstream TFBS that control transcription [38].

### III. MATERIALS AND METHODS

**Materials :** Autodock vina for molecular docking [39], Auto dock tool within MGL tool for pdbqt formation [39], VMD for extraction and visualization of protein [40], Open Babel for conversion of formats needed by different softwares [41], Desmond for viewing receptor ligand interactions [42].

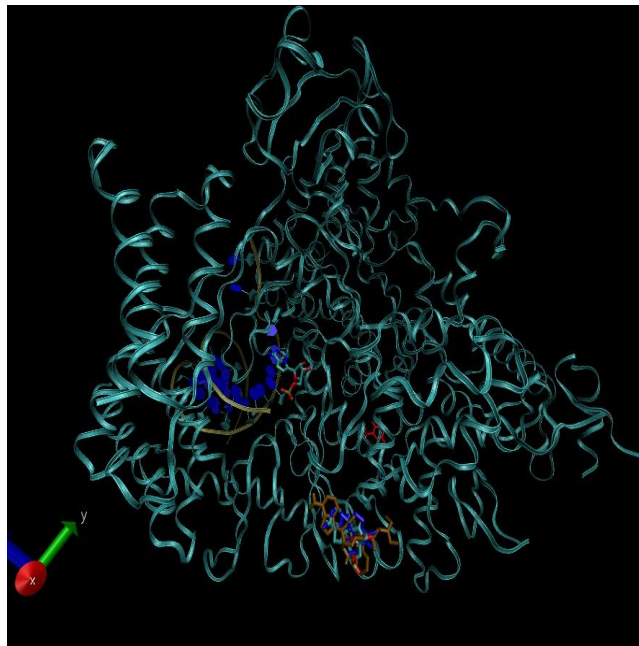
**Methods :** Download the 7bv2.pdb from protein category under the site “[www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)” [43], which is a nsp12-nsp7-nsp8 complex bound to the template primer RNA and triphosphate form of Remdesivir (RTP). Along with this Flavipiravir (492405.sdf), Remdesivir (121304016.sdf) has been downloaded from pubchem. The bounded ligand as F86 is extracted from 7bv2 through VMD software which is active remdesivir similar as Remdesivir triphosphate (GS-441524). After extracting the active remdesivir from 7bv2 through VMD, the modified protein structure named as 7bv2m1ig.pdb. Then above drugs are docked individually with the 7bv2m1ig.pdb with the mentioned spaces ( $2^{\text{nd}}$  space).

Figure :1



Dimensions of the grid box is  $x=22, y=26, z=28$  and centre of the grid box is  $x=93.095, y=94.155, z=115.574$ . After docking scoring values are analysed and the interacted residues are visualized in Desmond. **After docking of**

individual drug and taking the 1<sup>st</sup> conformation of those drug’s output then combine with 7bv2mlig.pdb. In the above Figure :1, it has been clearly observed the position of different ligands by different colours. Here original position of F86 within 7bv2 complex is showing little bit different than other three docked drugs (showing together) as extracted F86 (active form of Remdesivir, original cyan colour), Remdesivir (brown), beta-lapachone (yellow) and Flavipiravir (red) docked little bit far. Before this a 1<sup>st</sup> space docking shows the mostly same position occupied by above all three drugs, showing in Figure 2.



**Figure :2 (Above)** In the Figure:2, the docked position of all the above mentioned drugs has been able to find out the same position shown in the figure except Flavipiravir (Red colour). In this Figure :2, extracted F86 (Cyan colour), Remdesivir (Brown colour), Beta-lapachone (Blue colour) drugs are confirming the vina’s accuracy and also proving the ability of these drugs to find out the exact positions of the protein for interactions. In the 1<sup>st</sup> space docking the extracted F86 scored **-4.5** > **-5.3** of beta lapachone which means, 2<sup>nd</sup> one score much better than first one. It is also directly confirm the drugs shows the same kind of position’s affinities with the receptors mostly have the same kind of activity. 1st space docking scores also giving the idea of binding affinities of the different drugs Table :1.

#### IV. RESULTS AND DISCUSSION

After 2<sup>nd</sup> space docking the score of different drugs, getting from log table has been tabulized. After that combining of 1<sup>st</sup> conformation of different drugs with 7bv2mlig.pdb and the generated .pdb complex has been shown and analyzed through Desmond software. The generated .pdb complexe has named as “3rd-7bv2mlig-beta.pdb” for beta-lapachone molecule, “3rd-7bv2mlig-F86.pdb” for extracted F86, “3rd-7bv2mlig-Flavi.pdb” for Flavipiravir, “3rd-7bv2mlig

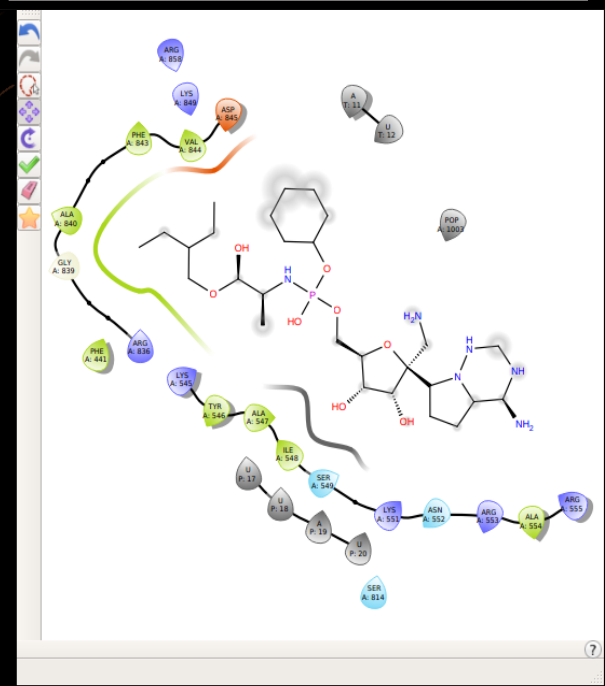
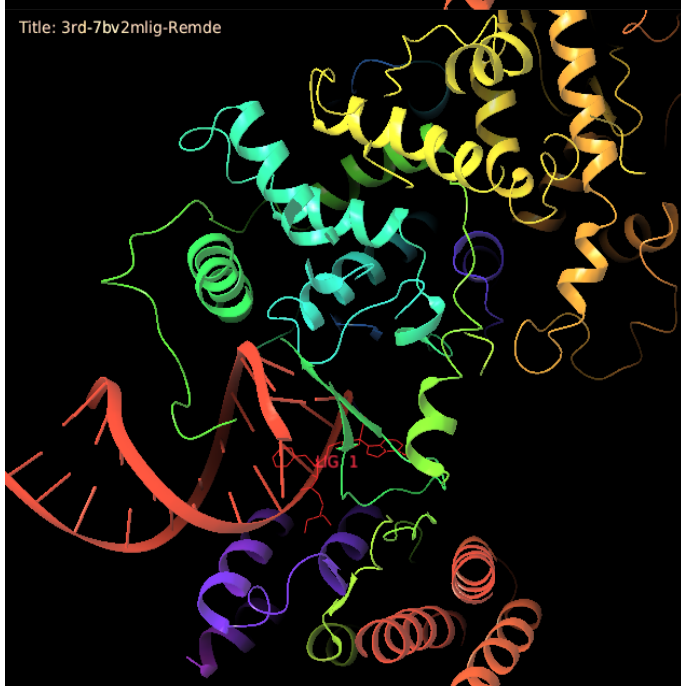
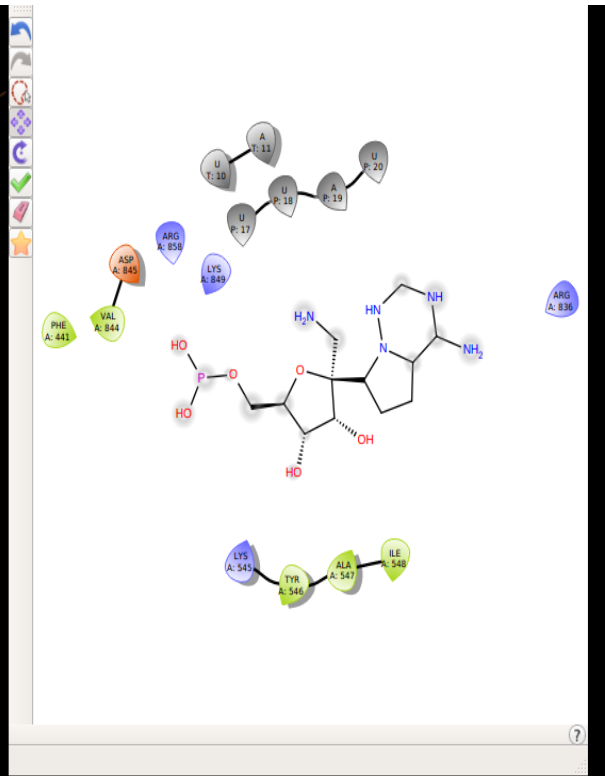
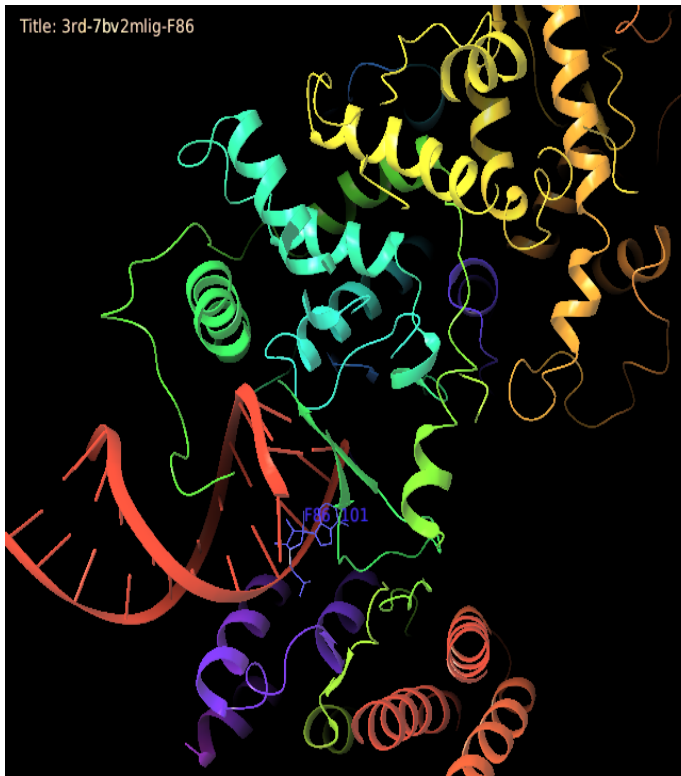
	1st Space	2nd Space															
7bv2-F86			ASP760	ASP623	ARG555	U10	A11	POP1003	MG1004	MG1005	U20	LYS545	THR687	ASN691			
7bv2mlig-F86	-4.5	-7.2	PHE441	VAL844	ASP845	ARG858	LYS849	U10	A11	U17	U18	A19	U20	LYS545	TYR546	ALA547	
7bv2mlig-beta	-5.3	-7.1	PHE441	VAL844	ASP845	ARG836	LYS849			U17	U18	A19	U20	LYS545		ALA547	
7bv2mlig-Remde	0.4	-8.6	PHE441	VAL844	ASP845	ARG836	LYS849	U12	A11	U17	U18	A19	U20	LYS545	TYR546	ALA547	
7bv2mlig-Flavi	-4.1	-5.4	PHE45	ALA46	PHE48	TYR129	LYS47	SER709	THR710	ASP711	LYS714	TYR32					
7bv2-F86			SER682														
7bv2mlig-F86	-4.5	-7.2	ILE548														
7bv2mlig-beta	-5.3	-7.1	ILE548	PHE843	ARG858												
7bv2mlig-Remde	0.4	-8.6	ILE548	PHE843	ARG858	POP1003	ALA840	SER549	LYS551	ASN552	ARG553	ALA554	ARG555	GLY839			
7bv2mlig-Flavi	-4.1	-5.4															

Table :1

-Remde.pdb” for Remdesivir molecule. Here in “3rd-7bv2mlig-Remde.pdb” complex the Remdesivir is GS-5734 Fig:4, which is not active form of Remdesivir (triphosphate of Remdesivir or GS-441524 equivalent of extracted F86 here) .

Figure :3 Below 1<sup>st</sup> Title:3rd-7bv2mlig-F86;

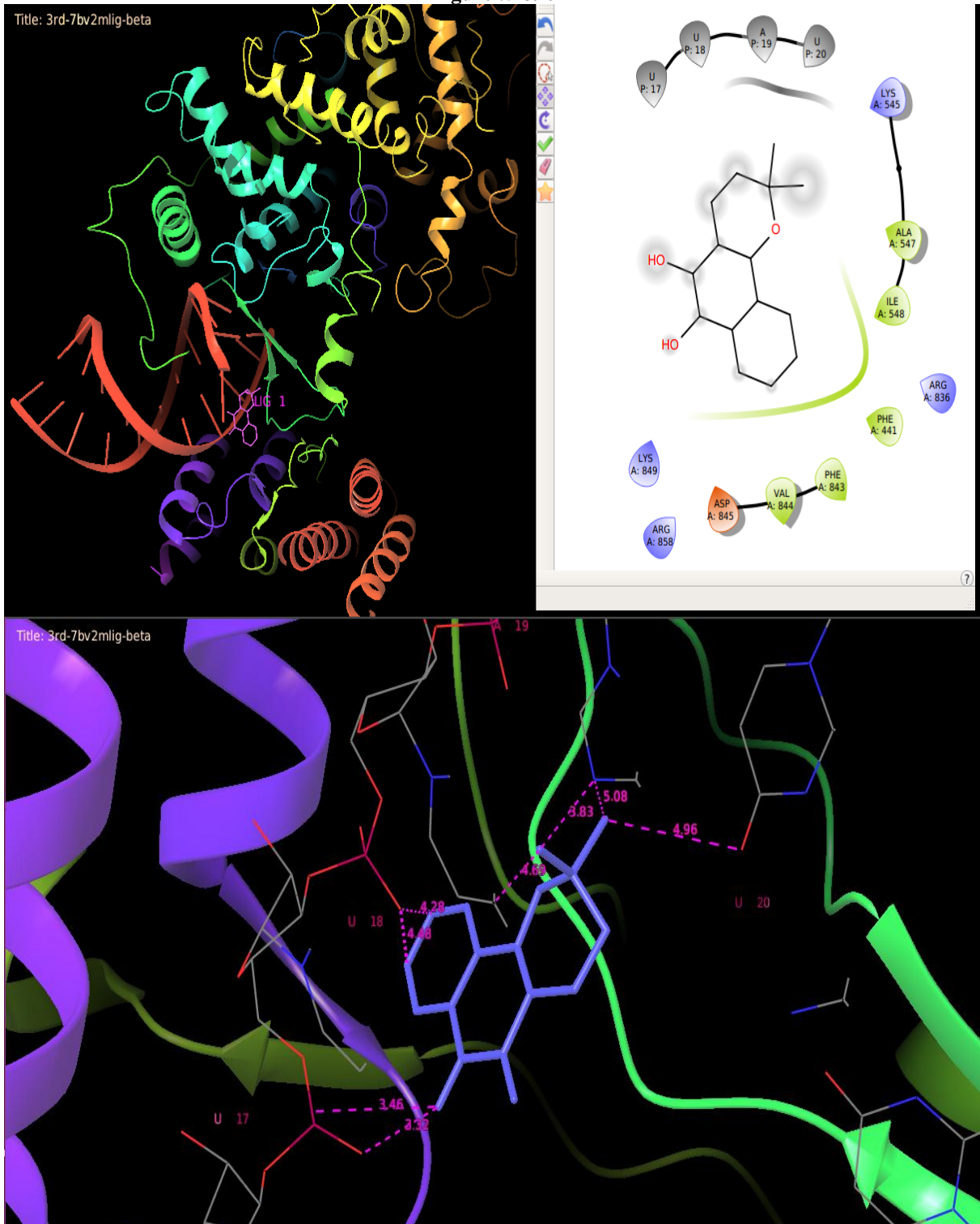
Figure :4 Below 2<sup>nd</sup> Title:3rd-7bv2mlig-Remde



In the 2<sup>nd</sup> space docking remdesivir scores best -8.6 and interacted residues also mentioned in the **Table :1** which shows number of interacted residues more than others which support the better score. But the active form of Remdesivir is F86 which scored -7.2, is more or less same as beta-lapachone’s score. The interacted residues showing in “Table 1”

after 2<sup>nd</sup> space docking clearly indicate that F86, Beta-lapachone and prodrug Remdesivir occupied the same pocket and interact with RdRp of covid19. The interacted residues shown in Figure :3,4 &5 also. The PHE441, VAL844, LYS545, ALA547, ILE548 created hydrophobic pocket and also ASP845, ARG836, LYS849, U17, U18, A19, U20 has been interacted by above mentioned three drugs, which support the findings of same position. The distance between U17 of RdRp and beta-lapachone are 3.32A and 3.46A, with U18 are 4.28A, 4.48A, with U20 is 4.96A, with U19 is 3.83A showing residues interact with beta-lapachone within 5A.

Figure :5 & 6



## V. CONCLUSION

The LTR of HIV-1 can be subdivided into the U3, R, and U5 regions, the first two of which are essential for transcription. Beta-lapachone is potent and selective inhibitor of HIV-1 LTR therefore inhibit the replication. Remdesivir acts early in infection, and decreases viral RNA levels. These and related mechanisms of action of remdesivir have been demonstrated in vitro for SARS-CoV, Ebola virus and MERS-CoV. A Replication of SARS-CoV-2 requires RdRp enzyme, a target of Remdesivir. The 7bv2.pdb structure of repository showing the binding of RdRp with triphosphate form of Remdesivir. RdRp is directly involved in the replication and transcription of RNA from an RNA strand. On the other hand Lopinavir is a highly potent inhibitor of the human immunodeficiency virus (HIV) protease essential for intracellular HIV assembly though in Wuhan, China with confirmed SARS-CoV-2 infection and COVID-19 pneumonia, oral administration of twice daily 400 mg lopinavir and 100 mg ritonavir for 14 days revealed rather disappointing results. So within this uncertainty, successful inhibition of RdRp with beta-lapachone is a new challenge to us and also for a chance of getting a nobel inhibitor of covid-19. In this project the modified 7bv2m1ig.pdb has been docked with different drugs spacially with beta-lapachone by vina given a satisfactory in silico score compare to other RdRp inhibitors (e.g. Remdesivir :-7.2, Beta-lapachone: -7.1). It is also directly confirm the drugs shows the same kind of position's affinity with the receptors mostly have the same kind of activity. Binding affinity, finding mostly same residues/pocket also support this chances. Drug repositioning may offer a strategy and a number of drugs have been repurposed, so after a satisfactory in silico results beta-lapachone demands for international clinical trials for SARS-CoV -2 at earliest.

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