Antiretroviral drug activity and potential for pre-exposure prophylaxis against COVID-19 and HIV infection

Dennis C. Copertino Jr., Bruno C. Casado Lima, Rodrigo R. R. Duarte, Timothy Wilkin, Roy M. Gulick, Miguel de Mulder Rougvie, and Douglas F. Nixon*

Division of Infectious Diseases, Weill Cornell Medicine, Cornell University, New York, NY, USA.

*Correspondence: Dr. Douglas F. Nixon, Division of Infectious Diseases, Weill Cornell Medicine, Cornell University, Belfer Research Building, Room 530, 413 E. 69th St., New York, NY, 10021, USA. E-mail: dnixon@med.cornell.edu

Abstract

COVID-19 is the disease caused by SARS-CoV-2, and has led to over 250,000 deaths by May 2020. Urgent studies to identify new antiviral drugs, repurpose existing drugs, or identify those drugs that can specifically target the overactive immune response are ongoing around the world. Antiretroviral drugs (ARVs) have been tested in past human coronavirus infections, and also against SARS-CoV-2, but a recent clinical trial of lopinavir and ritonavir failed to show any clinical benefit in COVID-19 disease. However, anecdotal reports suggest either reduced infection or a course of milder COVID-19 disease in people living with HIV (PLWH) on ARVs. We hypothesized ARVs other than lopinavir and ritonavir might be responsible for such effects. Here, we used chemoinformatic analyses to predict which ARVs would bind and potentially inhibit the SARS-CoV-2 main protease or RNA-dependent RNA polymerase enzymes, and identified a number of ARVs which bind to SARS-CoV-2 enzymes in silico. Our study identified HIV nucleoside/nucleotide analogue reverse transcriptase inhibitors (abacavir, emtricitabine, lamivudine, tenofovir, zidovudine), HIV protease inhibitors (ASC09, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir) and an HIV pharmacokinetic booster (cobicistat), as drug candidates with effective in silico binding to one or both viral enzymes. Tenofovir and emtricitabine are FDA-approved as HIV pre-exposure prophylaxis (PrEP) and have an extensive safety profile of use in populations without HIV. Existing or new combinations of antiretroviral drugs could potentially prevent or ameliorate the course of COVID-19, if shown to inhibit SARS-CoV-2 in vitro and/or in clinical trials. Further studies are needed to establish the activity of ARVs for treatment or prevention of SARS-CoV-2 infection.

Introduction

The novel coronavirus, now named SARS-CoV-2, was first reported as a new viral infection in humans in late 2019 and over the course of the past few months the virus has become a pandemic. Coronavirus disease, COVID-19, has in turn taken the lives of more than 250,000 people by May 2020, with hundreds of thousands of more deaths expected in the absence of effective treatments or additional control measures. COVID-19 presents a major worldwide public health emergency. Intense research efforts are underway to find effective antiviral treatments via novel drug design or drug repurposing (Sanders, Monogue, Jodlowski, & Cutrell, 2020) (Duarte et al., 2020) (Elmezayen, Al-Obaidi, Sahin, & Yelekci, 2020)

Some antiretrovirals (ARVs), normally used to treat HIV infection, have also been used in Hepatitis B virus (HBV) infection (Boettiger et al., 2016), and Amyotrophic Lateral Sclerosis (ALS) [NCT02437110]. ARVs have been studied both in vitro and in vivo for their activity against Severe Acute Respiratory Syndrome (SARS) (Chu et al., 2004; Yamamoto et al., 2004), and Middle East Respiratory Syndrome (MERS) (de Wilde et al., 2014), which led to adoption of two ARVs, lopinavir and ritonavir, as putative antiviral drugs against SARS-CoV-2. However, a small randomized controlled clinical trial of lopinavir and ritonavir co-administered to hospitalized adults with severe COVID-19 showed no clinical benefit over the standard of care (Cao et al., 2020). A recent preprint reported that tenofovir and emtricitabine act as chain terminators in the replication of viral RNA by the SARS-CoV-2 RdRp (Jockusch et al., 2020). In silico studies help us to gauge projected mechanisms and likely molecules which bind to solved targets, in a cost effective, high throughput manner, ideal for primary analyses. In vitro studies provide necessary details for effective inhibitory concentrations of each compound tested, and clinical studies would provide further evidence for effectiveness in people.

We used a comprehensive in silico docking analysis of ARVs to catalytically active sites within the Main protease (Mpro) and RNA dependent RNA polymerase (RdRp) of SARS-CoV-2, in order to understand which HIV ARVs might bind and potentially inhibit SARS-CoV-

2, and at which specific part of the viral replication cycle. We hypothesized that ARVs would show activity against SARS-CoV-2, and used a small molecule docking algorithm with an empirical scoring function, $PLANTS_{chemplp}$ (Korb, Stutzle, & Exner, 2009) to identify a number of ARVs which we believe should be studied further, either individually or in combination, for anti-SARS-CoV-2 activity. Drugs identified to bind the catalytic site of the SARS-CoV-2 Mpro were the HIV protease inhibitors ASC09, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir and the HIV pharmacokinetic (PK) booster cobicistat. The drugs shown to bind to the catalytic site of the RdRp include, nucleoside or nucleotide reverse transcriptase inhibitors abacavir, emtricitabine, lamivudine, tenofovir, zidovudine, the protease inhibitors ASC09, atazanavir, indinavir, lopinavir, ritonavir and saquinavir, and a PK booster, cobicistat.

In order to better understand the impact of ARVs on COVID-19 infection or disease course, people living with HIV (PLWH) or people at risk of HIV infection on pre-exposure prophylaxis (PrEP) could provide critical insights into the course of COVID-19 disease. Anecdotal reports show that PLWH on ARVs can be COVID-19 infected (Blanco et al., 2020), but of the first 543 people admitted to a hospital in Barcelona with the SARS-CoV-2, only five were PLWH. Additional in vitro studies and clinical trials are needed to understand whether existing ARV regimens might protect against SARS-CoV-2 infection or ameliorate COVID-19 in PLWH. We attempted to estimate the number of PLWH at risk of death from COVID-19 by August 4_{th} 2020 in the USA and in each state. Therein, we sought to estimate a benchmark for which observational studies could use to measure actual deaths of PLWH by COVID-19, and compare it to the expected number of deaths noted in **Supplemental Table 1**.

As COVID-19 infection is such a rapidly changing problem, prospective placebo-controlled studies in appropriate groups would be preferable to observational studies. However, in silico and in vitro work can often save time and effort in screening effective drugs, in a high throughput manner. Therefore, we sought to use in silico methods to determine whether existing ARVs might bind to key SARS-CoV-2 viral enzymes and inhibit viral replication in doing so. Our results suggest that some commonly used ARVs have binding potential in silico to SARS-CoV-2 including ARVs commonly given to people without HIV as

PrEP or treatment of chronic HBV. Further studies should explore activity of ARVs in vitro, in animal models, and in clinical trials, to assess whether the ARVs we identified could be used either in COVID-19 treatment regimens or as pre-exposure prophylaxis for SARS-CoV-2 infection.

Methods

Protein-Ligand Small Molecule Docking with PLANTS

Two of the optimal nonstructural protein targets within the SARS-CoV-2 virus are the Main protease (Mpro) and the RNA dependent RNA polymerase (RdRp). Small molecules which might inhibit these two proteins would bind to key residues typically required for the enzymatic activity of these proteins. For small molecules to effectively inhibit the activity of the Mpro it should disrupt the substrate binding site, marked by residues Gln189, His41 or Cys145 (Zhang et al., 2020). For the RdRp, the substrate binding site is marked by conserved residues amongst polymerases 759-SDD-761, within Motif Cs residues, 753-FSMMILSDDAVVCFN-767 (Gao et al., 2020). In order to identify compounds which are predicted to effectively and specifically bind to these catalytic sites of the Mpro, and RdRp, we performed in silico molecular docking analyses using the PLANTS software against a database of FDA-approved small molecules (Korb et al., 2009) (Douguet, 2018). From the database of small molecules, we manually extracted all HIV antiretrovirals for discussion. Docking simulations using the main protease (Mpro) (Protein Data Bank [PDB] ID: 6Y2E), and the RNA-dependent RNA polymerase (RdRp) (PDB ID: 6M71) of SARS-Cov-2, using the Protein-Ligand ANT System (PLANTS) (Korb et al., 2009), accessed via https://chemoinfo.ipmc.cnrs.fr/ (Douguet, 2010). The ligand docking sites were specified as the catalytically active sites by Zhang et al. (Zhang et al., 2020) and Gao et al. (Gao et al., 2020), using a radius of +10 Å around the assigned residues, while the weight in final score for the protein structures was 1, and all remaining settings were set to the default setting. Protons are added to the structure using the PDB2PQR with an AMBER forcefield option (Dolinsky, Nielsen, McCammon, & Baker, 2004). The

resulting protein-ligand scores (PLANTS scores) were calculated using the empirical scoring algorithm, CHEMPLP (Douguet, Munier-Lehmann, Labesse, & Pochet, 2005), and reflect the energy change when ligands and proteins come together, with values more negative than (-91.00) suggesting likely protein-ligand interactions. All other settings were set to their default parameters. Protein-ligand structures were visualized using PyMol 2.3.5. For the entirety of this paper we will use the terminology ARVs to describe all of the tested drugs, including the PK booster cobicistat, although cobicistat does not have anti-HIV activity perse, and therefore should not truly be considered an HIV ARV. Structures from the FDA approved library did not include the metabolically active structures for some of the HIV nucleoside (or nucleotide) analogue reverse transcriptase inhibitors (NRTIs), nor any unapproved drugs such as ASC09. The biologically active structures of these drugs were obtained from PubChem (Kim et al., 2019) or other sources noted in **Supplementary Table 2**. The active triphosphorylated NRTIs were then run against each of the viral enzymes individually using the same software and settings stated above. The image portrayed in **Figure 1** was created using Biorender.

Results

Molecular docking analyses

We ran analyses to predict the ability of HIV ARV drugs to bind to the catalytic sites of the SARS-CoV-2 main protease (Mpro) and RNA-dependent RNA polymerase (RdRp) enzymes, corroborating their repurposing potential, and providing a possible mechanism of action involving direct interactions with viral components (**Figure 1**). The $PLANTS_{chemplp}$ scores calculated here reflect the energy change when the drug comes together with the catalytic site of either the Mpro or RdRp with more negative numbers suggesting a more likely drug-protein interaction (**Table 1**). HIV ARVs with scores lower than -91 with predicted binding to the Mpro include PIs, ASC09, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; and the PK booster, cobicistat. HIV ARVs with scores lower than -91 with predicted binding to the RdRp include NRTIs, abacavir, emtricitabine, lamivudine, tenofovir, and

zidovudine; PIs, ASC09, atazanavir, indinavir, lopinavir, ritonavir, and saquinavir; and the PK booster cobicistat. **Figure 2** depicts the Mpro and RdRp designated active sites for the purpose of this analysis. **Figure 3** depicts select molecules docking with the Mpro. **Figure 4** depicts select molecules docking with the RdRp.

Estimates of COVID-19 and HIV infection

There are several important issues that complicate the issue of COVID-19 and HIV. PLWH of color are disproportionally impacted by COVID-19. Half of the PLWH in the USA are over 50 years of age, and co-morbidities are more common in this group. We estimated the number of PLWH at risk for death from COVID-19 in the USA by August 4th 2020, based upon projected estimates (**Supplemental Table 1**). These estimates are confounded by many variables, and since the mortality rates are fluctuating with changing testing algorithms, and data availability, they are limited in utility, yet in order to make sense of data in any observational study, such numbers need to be estimated. An observational study to determine the incidence or disease course from SARS-CoV-2 infection in PLWH who take ARV therapy, compared to those that do not is technically challenging, and problematic because ARV therapy is considered the standard of care for HIV, worldwide. A prospective, randomized study of anti-HIV PrEP medications to prevent COVID-19, would be more appropriate. In addition, linking COVID-19-related deaths to HIV registries could provide some of these insights as well.

Discussion

The data presented here, along with anecdotal evidence and recent in vitro studies, present a case for the possible prevention and treatment of COVID-19 with repurposed HIV Antiretroviral drugs (ARVs). ARVs were studied in past human coronavirus infections of SARS-CoV and MERS (Ford et al., 2020), and are being used in SARS-CoV-2 clinical trials

as listed in **Table 2**. Anecdotal initial reports suggest less infection and a milder course of COVID-19 in people living with HIV (PLWH). However, a recent small clinical trial of lopinavir and ritonavir failed to show any clinical benefit in people with severe disease (Cao et al., 2020). Here, we used chemoinformatic analyses to predict which ARVs would bind to the SARS-CoV-2 Mpro or RdRp enzymes, and identified a number which bound to either or both. Existing or new combinations of ARV regimens for preventing or treating HIV infection could potentially prevent or ameliorate the course of COVID-19. Further studies are needed to establish the value of ARVs in COVID-19.

Previous published works discuss the similarities between RdRp's from previous coronaviruses, and HIV reverse transcriptase (RT) (Oberg, 2006). More recent publications compared the SARS-CoV viral enzymes with enzymes from SARS-CoV-2. The identity between the SARS-CoV and SARS-CoV-2 Mpro is 96% (Chen, Yiu, & Wong, 2020), and identity between SARS-CoV and the SARS-CoV-2 RdRp 96%, with their similarity being 98% (Shannon et al., 2020). The similarity between the enzymes of SARS-CoV and SARS-CoV-2 is marked, and provides rationale for testing drugs which were effective in vitro against SARS-CoV, like lopinavir and ritonavir (Chu et al., 2004), in the setting of SARS-CoV-2, as experimental therapies.

In our study, patterns of HIV inhibitor type seem to correspond closely with each viral enzyme. For example, the ARVs predicted to bind to the Mpro were PIs and cobicistat. ARVs with predicted binding to the RdRp were in the nucleoside and nucleotide reverse transcriptase inhibitor (NRTI), protease inhibitor (PI) families, and the PK booster cobicistat. Cobicistat is a CYP3A inhibitor (L. Xu et al., 2010) used in the treatment of HIV, and is an analog of ritonavir which has proven dual mechanisms as a PI and CYP3A inhibitor, and both share a near exact structure with the exception of 5 atoms (Kumar et al., 1999). Cobicistat's ability to inhibit CYP3A gives it the colloquial name of "booster". Mechanistically, cobicistat inhibits CYP3A activity in the liver which is typically used to metabolize certain drugs including most PIs. Thus, for it to have a boosting effect on a drug, the active form of the drug/molecule must be mostly or partly broken down by the CYP3A enzyme in the liver. Cobicistat's in silico binding to the

Mpro and RdRp follows closely with other PIs, of which it is an analog. Therefore, it may have anti-COVID-19 activity itself, despite no reported protease activity to date. Due to cobicistat's effective in silico docking to both the SARS-Cov-2 Mpro and RdRp it should be tested in vitro and if effective, potentially in clinical trials. However, widespread use of protease inhibitors would be challenging to implement because of adverse drug-drug interactions and tolerability issues. We (in this study), and others, have shown that PIs bind to the RdRp of SARS-Cov-2 in silico (Beck, Shin, Choi, Park, & Kang, 2020), but we do not yet understand why this binding occurs. Further in vitro work will be key to elucidating the ability of PIs to bind both the RdRp and Mpro of SARS-CoV-2.

Remdesivir, an investigational nucleotide/adenosine analogue currently in clinical studies for COVID-19 has been shown to have potential activity against RdRp of SARS-CoV-2 (Gordon et al., 2020). Remdesivir is an adenosine analog, and acts on the RdRp by being incorporated into the growing RNA strand and inhibiting further viral transcription. Remdesivir is the first agent to show preliminary clinical efficacy in an NIH randomized, placebo-controlled study (Wang et al., 2020) and the FDA has approved its Emergency Use Authorization for hospitalized patients with severe COVID-19. Tenofovir and emtricitabine can inhibit the RdRp of SARS-CoV-2 in vitro (Jockusch et al., 2020), and expected from our in silico analyses. Taken together these studies confirm that both nucleotide analogs and nucleoside analogs can be incorporated into growing RNA strands and thus may act as chain terminators of growing viral RNA strands under replication by the RdRp, likely due to the low fidelity of the RdRp to its substrate (Jockusch et al., 2020; McKenna, Kashemirov, Peterson, & Goodman, 2010). The remaining NRTIs, if effective against COVID-19, could confer protection through the same mechanism. This suggests at least that PLWH on a backbone regimen of tenofovir and emtricitabine could be partially protected from SARS-CoV-2 infection or COVID-19 disease, although only additional in vitro studies and clinical trials could confirm this. Our work would also suggest that patients taking abacavir and lamivudine could be protected from COVID-19 by inhibition of the RdRp, but again, in vitro work and clinical trials are needed to confirm this. Integrase inhibitors in our study were scored in the -79 to -89 $PLANTS_{chemplp}$

range. These scores are harder to interpret, but at a minimum do warrant further study in vitro and in clinical trials.

Recently the first ever two-drug HIV regimens have been approved for PLWH, including Dovato® (ViiV) dolutegravir and lamivudine, an integrase inhibitor and an NRTI, respectively. The other approved two drug regimen, Juluca® (ViiV), includes dolutegravir and rilpivrine. Observational studies of COVID-19 disease course of different drug combinations are critical for those living with HIV worried about contracting SARS-CoV-2, or acquiring the virus and navigating COVID-19 disease. These questions can only be answered by further in vitro research, observational studies, and clinical trials.

It is to be expected that NNRTIs as a class did not bind well to the catalytic site for the SARS-CoV-2 RdRp, which is the nucleoside/nucleotide triphosphate (NTP) binding site, where elongation of the RNA strand occurs (Gao et al., 2020). When NRTIs are metabolized and form triphosphate structures, they are capable of being added to the growing RNA/DNA strand and chain termination will follow (Gordon et al., 2020; Jockusch et al., 2020; Wang et al., 2020). However, HIV reverse transcriptase is inhibited by NNRTIs at a site different from that which the NRTIs bind to. Instead, NNRTIs inhibit HIV RT in a non-competitive fashion, binding at a site distant from the polymerase active site, usually stopping key protein-protein interactions from occurring, or changing the active site structure (Sluis-Cremer & Tachedjian, 2008). Past studies have found no potential homologous hydrophobic NNRTI binding site on the previous SARS-CoV RdRp structure (X. Xu et al., 2003), although we identified potential hydrophobic pockets on the surface of the RdRp (data not shown). This will remain an area for further research to address, though COVID-19 research should certainly include second generation NNRTIs with more rotatable bonds and flexibility.

Our data suggest select ARVs could also be tested as pre-exposure prophylaxis (PrEP) for COVID-19, if in vitro efficacy was shown. Drugs used for HIV PrEP (tenofovir/ emtricitabine; Truvada® or Descovy®, Gilead) are well tolerated (Charles B. Hare, 2020), and, if effective against SARS-CoV-2 in vitro, studies in trials would be more easily justified given the excellent tolerability, lack of drug-drug interactions, and well characterized safety profile,

when compared to PIs. We know of one randomized, placebo-controlled study of SARS-CoV-2 prophylaxis with tenofovir disoproxil fumarate/emtricitabine vs. hydroxychloroquine vs. both (vs placebo) in health care workers in Spain (N=4000) NCT04334928.

At this time the authors of this study would like to caution that this report has not made any conclusion or recommendation on any drug regimen change. However, our studies suggest that further investigations of the role of ARVs in SARS-CoV-2 prevention or amelioration of COVID-19 disease are warranted.

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Drug Name	RDRP PLANTS score	Mpro PLANTS score	Drug Class
Abacavir[1]	**-107.19**	-80.99	NRTI
Cobicistat	**-106.57**	**-108.7**	CYP3A Inhibitor
Emtricitabine[1]	**-106.22**	-80.84	NRTI
Atazanavir	**-99.33**	**-105.72**	PI
Saquinavir	**-98.68**	**-107.57**	PI
Ritonavir	**-97.79**	**-111.52**	PI
Zidovudine[1]	**-96.59**	-76.33	NRTI
Lamivudine[1]	**-95.23**	-78.73	NRTI
Indinavir	**-94.83**	**-103.47**	PI
Lopinavir	**-94.55**	**-96.47**	PI
ASC09[3]	**-92.46**	**-100.31**	PI
Tenofovir[1]	**-91.16**	-75.77	NRTI
Darunavir	-88.76	-87.9	PI
Nelfinavir	-86.22	**-94.98**	PI
Amprenavir	-85.13	-88.07	PI
Maraviroc	-84.44	-90.46	FI
Tipranavir	-83.84	**-99.2**	PI
Bictegravir	-81.93	-84.99	INSTI
Raltegravir	-81.08	-85.61	INSTI
Elvitegravir	-80.62	-89.42	INSTI
Dolutegravir	-78.4	-79.49	INSTI
Delavirdine	-75.24	-75.27	NNRTI
Etravirine	-73.13	-73.51	NNRTI
Efavirenz	-71.94	-66.03	NNRTI
Rilpivrine	-70.41	-77.66	NNRTI
Tenofovir[2]	-69.54	-62.65	NRTI
Abacavir[2]	-68.57	-74.97	NRTI
Doravirine	-67.97	-70.19	NNRTI
Emtricitabine[2]	-64.28	-69.82	NRTI
Nevirapine	-64.08	-68.18	NNRTI
Lamivudine[2]	-62.76	-67.67	NRTI
Zidovudine[2]	-49	-64.37	NRTI

[1]Active Form, Triphosphorylated/Diphosphorylated; [2]Inactive form: No additional phosphate groups; [3]ASC09 is also referred to as TMC-310911and is currently not FDA approved; RDRP: RNA-dependent RNA polymerase; Mpro: Main protease; NRTI: Nucleoside/Nucleotide Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor; FI: Fusion Inhibitor

Table 1. Docking scores for HIV drugs tested against SARS-CoV-2 RdRp and Mpro. The HIV ARV inhibitor class is also referenced.

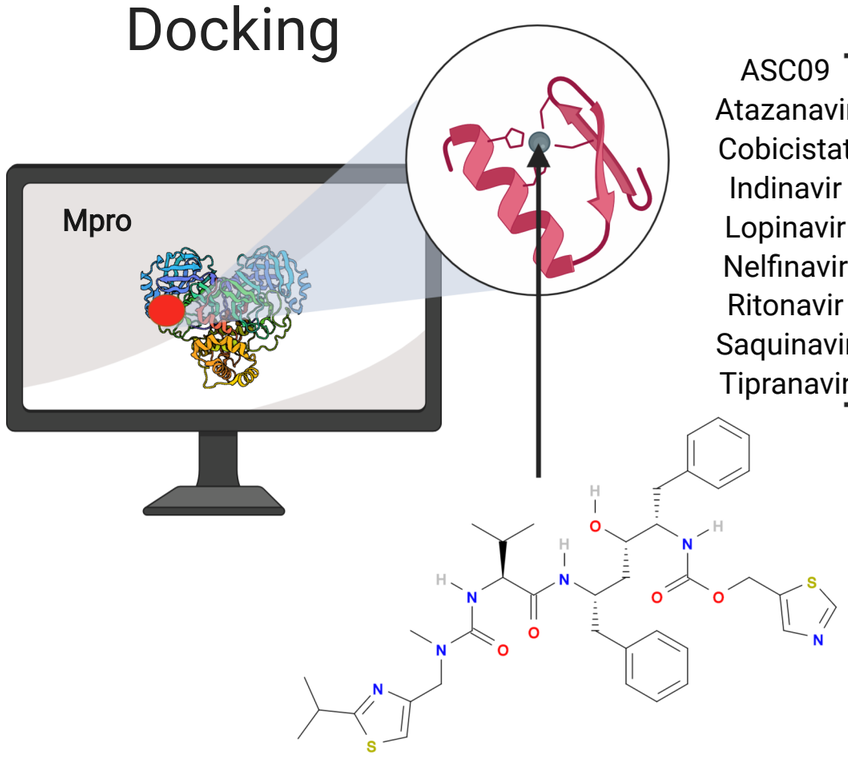
Clinical Trial Number	Conditions	Interventions
NCT04328012	COVID-19	**Lopinavir/ritonavir**, Hydroxychloroquine Sulfate, Losartan, Placebos
NCT04333953	COVID-19 HIV/AIDS	Other: No intervention
NCT04321993	COVID-19	**Lopinavir/ritonavir**, Hydroxychloroquine sulfate, Baricitinib (janus kinase inhibitor), Sarilumab (anti-IL-6 receptor)
NCT04343768	COVID-19	Hydroxychloroquine, **Lopinavir / Ritonavir**, Interferon Beta-1A, Interferon Beta-1B
NCT04328285	COVID-19	Hydroxychloroquine, Placebo of Hydroxychloroquine, **Lopinavir and ritonavir**, Placebo of **LPV/r** Tablets
NCT04350671	COVID-19	Interferon Beta-1A, **Lopinavir / Ritonavir**, Single Dose of Hydroxychloroquine
NCT04350684	COVID-19	Umifenovir, Interferon-Œ≤ 1a, **Lopinavir / Ritonavir**, Single Dose of Hydroxychloroquine, Standards of Care
NCT04330690	COVID-19	**Lopinavir/ritonavir,** hydroxychloroquine, remdesivir
NCT04307693	COVID-19	**Lopinavir/ritonavir**, Hydroxychloroquine sulfate
NCT04331470	COVID-19	Levamisole Pill + Budesonide+Formoterol inhaler, **Lopinavir/Ritonavir** + hydroxychloroquine
NCT04346147	COVID-19 Pneumonia	Hidroxycloroquine, **Lopinavir/ritonavir**, Imatinib tablets, Baricitinib Oral Tablet
NCT04345276	COVID-19	Danoprevir+**Ritonavir**
NCT04291729	COVID-19	Ganovo+**ritonavir**+/-Interferon nebulization
NCT04286503	COVID-19	Carrimycin, **lopinavir/ritonavir** tablets or Arbidol or chloroquine phosphate, basic treatment
NCT04255017	COVID-19	Abidol hydrochloride, Oseltamivir, **Lopinavir/ritonavir**
NCT04261270	COVID-19 Pneumonia	**ASC09F**+Oseltamivir, **Ritonavir**+Oseltamivir, Oseltamivir
NCT04295551	COVID-19	**Lopinavir / ritonavir** tablets combined with Xiyanping injection, **Lopinavir/ritonavir treatment**
NCT04334928	COVID-19	**Emtricitabine/tenofovir disoproxil**, Hydroxychloroquine, Placebo: Emtricitabine/tenofovir disoproxil Placebo, Placebo: Hydroxychloroquine
NCT04315948	COVID-19	Remdesivir, **Lopinavir/ritonavir**, Interferon Beta-1A, HydroxychloroquineOther: Standard of care
NCT04252274	Pneumonia, Pneumocystis Coronavirus	**Darunavir and Cobicistat**
NCT02735707	Community-acquired Pneumonia, Influenza, COVID-19	Fixed-duration Hydrocortisone, Shock-dependent hydrocortisone, Ceftriaxone, Moxifloxacin or Levofloxacin, Piperacillin-tazobactam, Ceftaroline, Amoxicillin-clavulanate, Macrolide administered for 3-5 days, Macrolide administered for up to 14 days, Five-days oseltamivir, Ten-days oseltamivir, **Lopinavir/ritonavir**, Hydroxychloroquine, Hydroxychloroquine + **lopinavir/ritonavir**, Interferon-Œ≤1a, Anakinra, Fixed-duration higher dose Hydrocortisone, Tocilizumab, Sarilumab
NCT04321174	COVID-19 PrEP	**Lopinavir/ritonavir**
NCT04261907	COVID-19	**ASC09/ritonavir group, lopinavir/ritonavir group**
NCT04275388	COVID-19 Pneumonia	Xiyanping injection, **Lopinavir / ritonavir**, alpha-interferon nebulization
NCT04251871	COVID-19 Pneumonia	Conventional medicines (Oxygen therapy, alfa interferon via aerosol inhalation, and **lopinavir/ritonavir**) and Traditional Chinese Medicines (TCMs) granules, Conventional medicines (Oxygen therapy, alfa interferon via aerosol inhalation, and **lopinavir/ritonavir**)
NCT04351724	COVID-19	Chloroquine or Hydroxychloroquine, **Lopinavir/Ritonavir** Other: Best standard of care, Rivaroxaban, Thromboprophylaxis, Candesartan, non-RAS blocking antihypertensives, Clazakizumab, placebo for clazakizumab
NCT04276688	COVID-19	**Lopinavir/ritonavir**, Ribavirin, Interferon Beta-1B

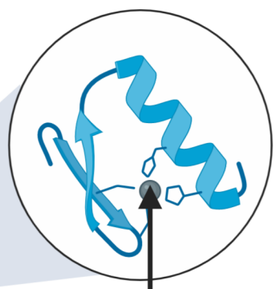
NCT04278404	COVID-19, multiple other conditions	The POP02 study is collecting bodily fluid samples (i.e., whole blood, effluent samples) of children prescribed the following drugs of interest per standard of care: Oseltamivir, Oxycodone, Risperidone, Sertraline, Zolpidem, Dextroamphetamine /Amphetamine, Azithromycin, Chloroquine, Hydroxychloroquine, **Lopinavir/Ritonavir**, Ribavirin, (+54 other drugs of interest not listed here)
NCT04359095	COVID-19	Hydroxychloroquine, **Lopinavir / Ritonavir Pill**, Azithromycin, Standard treatment
NCT04364022	Prevention of COVID-19	Hydroxychloroquine Sulfate 200 MG [Plaquenil], **Lopinavir/ritonavir**
NCT04372628	COVID-19	Hydroxychloroquine, **Lopinavir/ritonavir 400 mg/100 mg**, Placebo
NCT04366245	COVID-19	Hyperimmune plasma, Hydroxychloroquine + Azithromycin or **Lopinavir/ritonavir** + Interferon β-1b + Hydroxychloroquine
NCT04365582	COVID-19	Azithromycin, Hydroxychloroquine, **Lopinavir 200Mg/Ritonavir 50Mg Tab**
NCT04373044	COVID-19, multiple other conditions (10+)	Baricitinib, Hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir

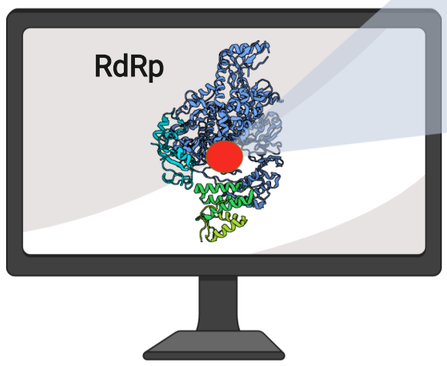
Table 2. Clinical trials with approved and experimental HIV ARVs included in the trial as treatment for COVID-19. HIV ARV drugs used in each clinical trial are in bold.

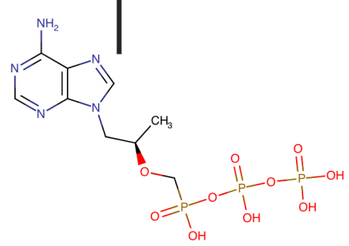
A.

PLANTS Molecular Docking



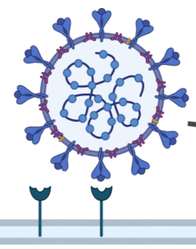






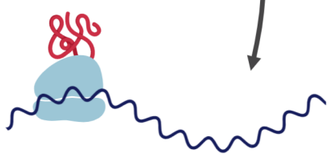
ASC09
Atazanavir
Cobicistat
Indinavir
Lopinavir
Nelfinavir
Ritonavir
Saquinavir
Tipranavir

SARS-CoV-2

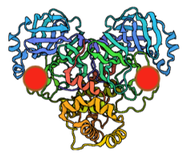


Cytoplasm

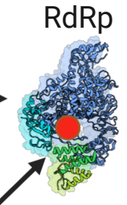
Host Ribosome



Translation of Viral RNA

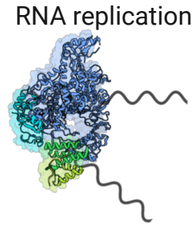


Polyprotein pp1ab uncleaved



RdRp

Inhibition of RNA replication



Genomic replication

Subgenomic (nested) transcription

Nucleocapsid (N)

Spike (S)

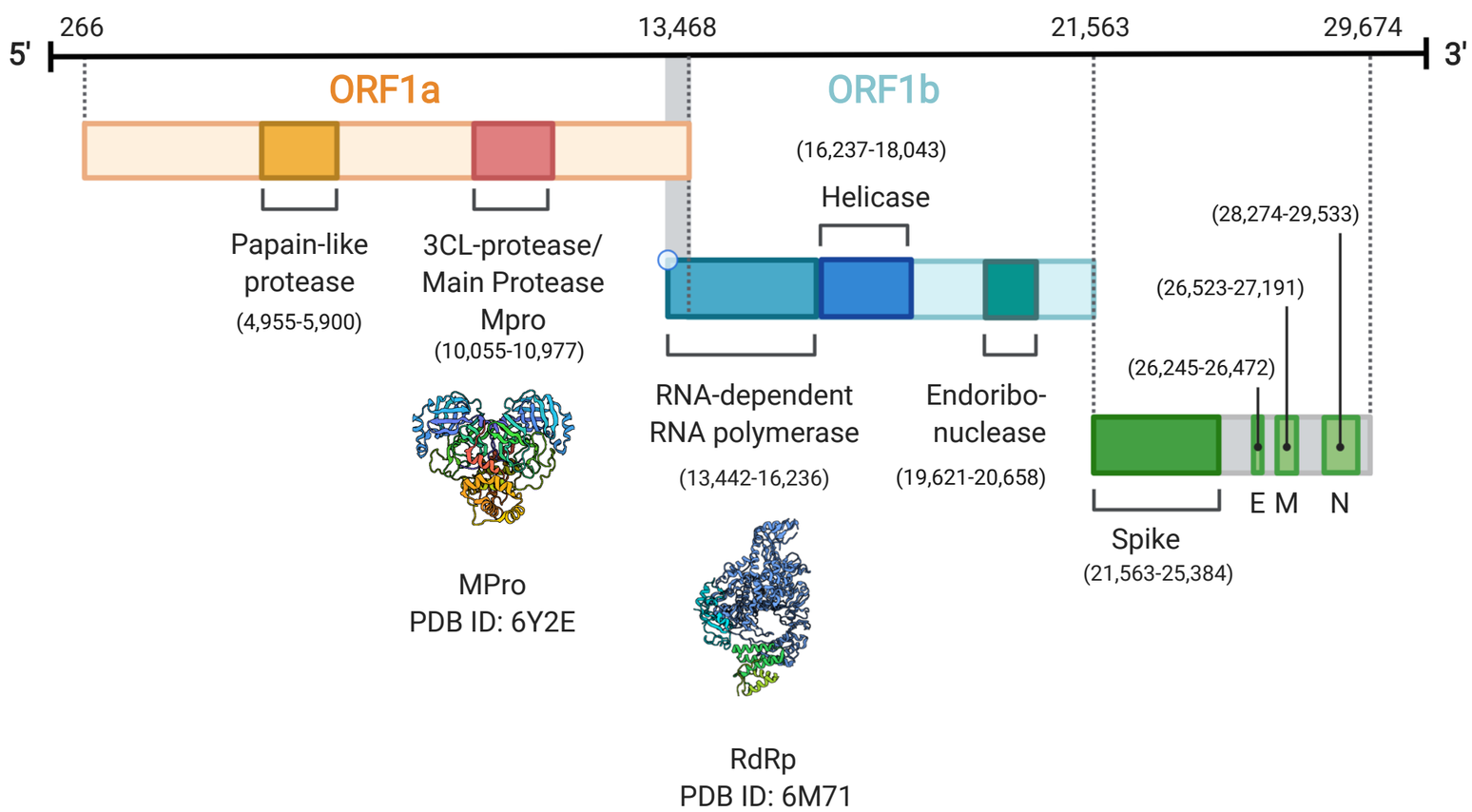
Membrane (M)

Envelope (E)

Abacavir
Emtricitabine
Lamivudine
Tenofovir
Zidovudine

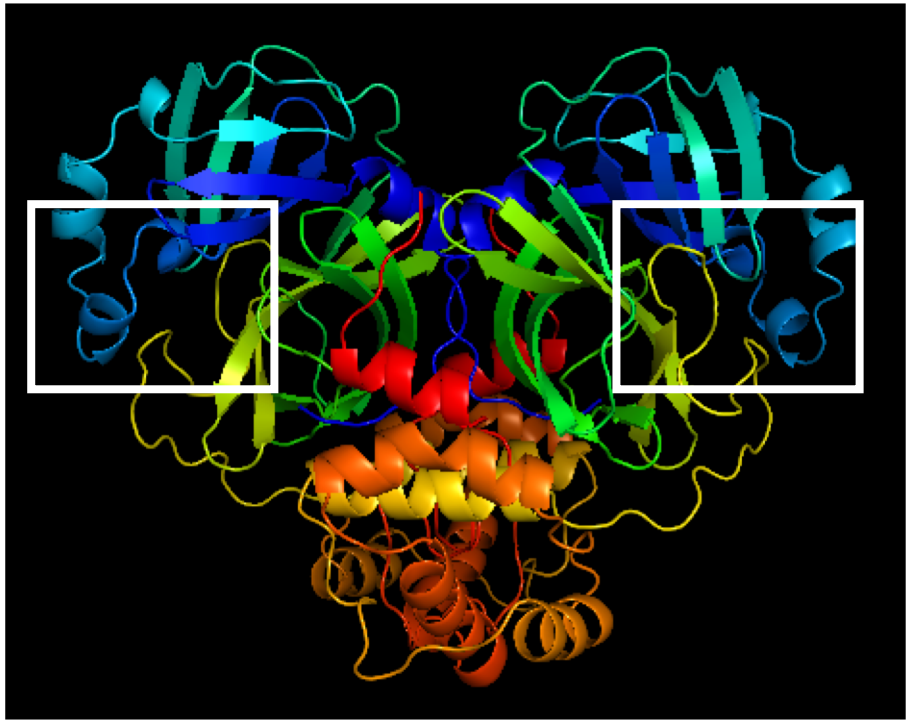
ASC09
Atazanavir
Cobicistat
Indinavir
Lopinavir
Ritonavir
Saquinavir

B.



MPro
PDB ID: 6Y2E

RdRp
PDB ID: 6M71



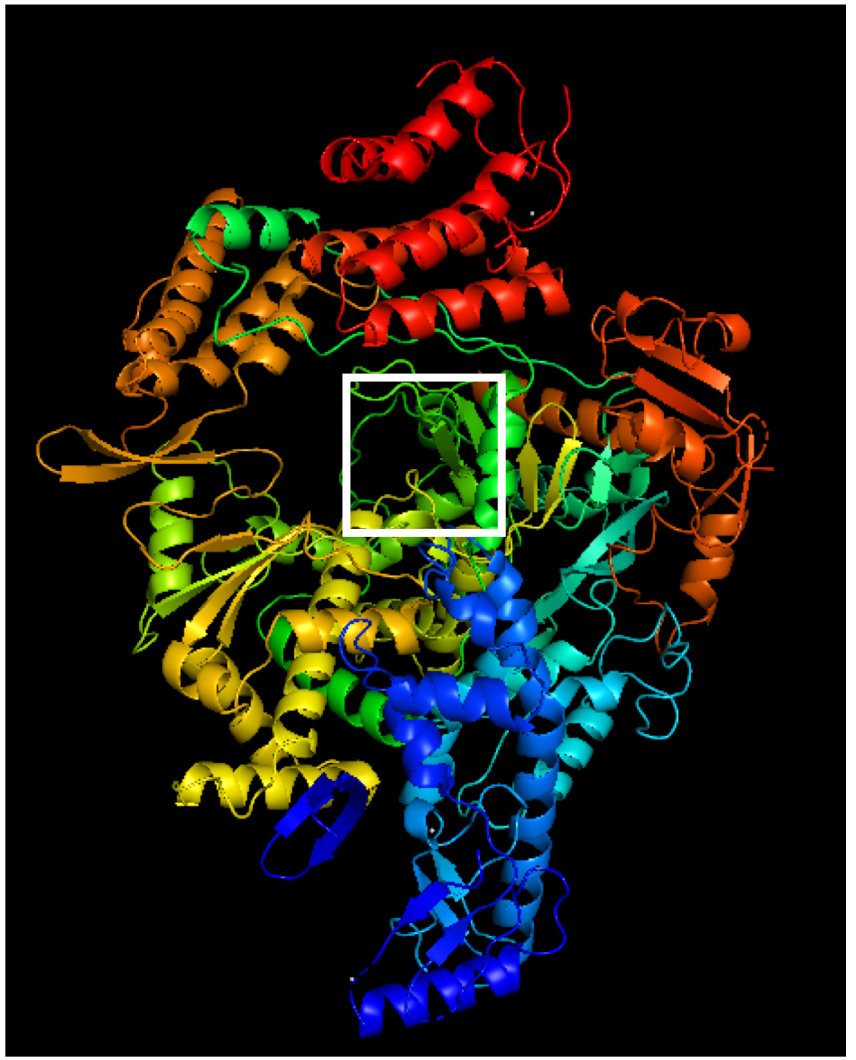
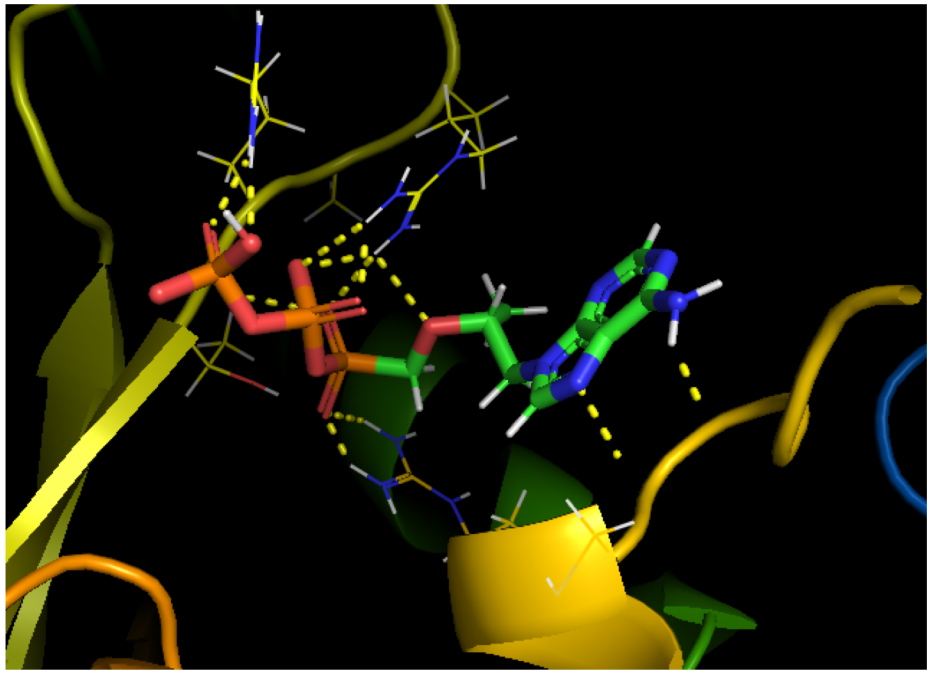
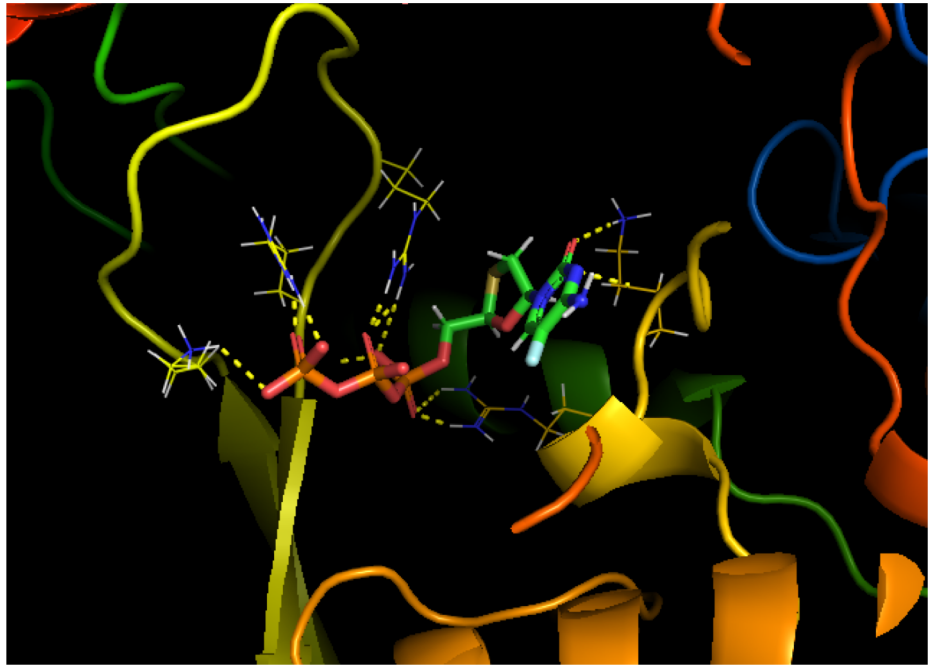
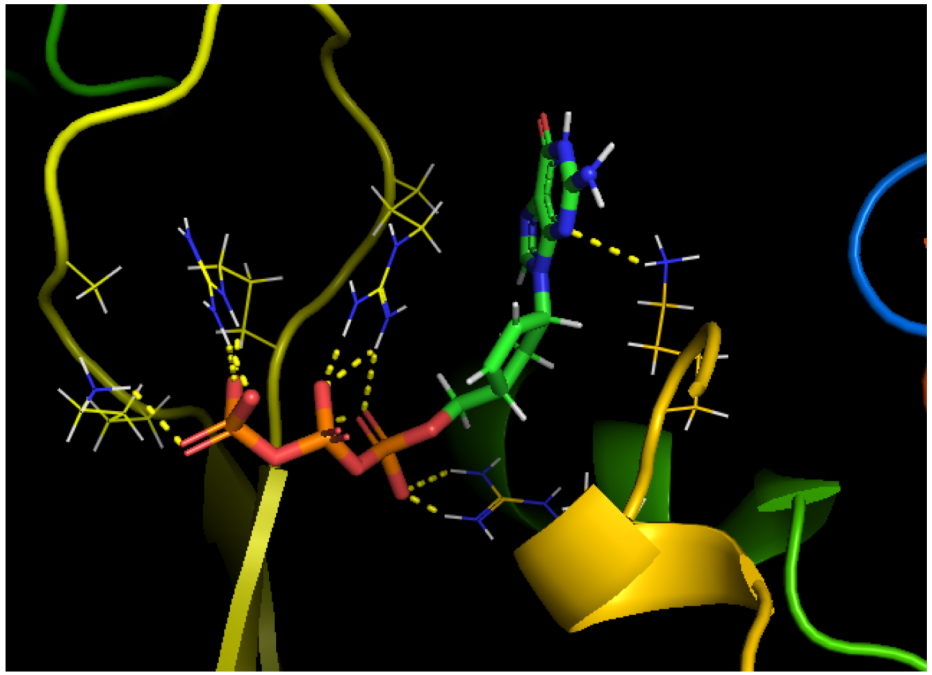


Figure 2. Image of the Main Protease (Mpro, left) and RNA-dependent RNA Polymerase (RdRp, right) of SARS-CoV-2, catalytic sites are inside white boxes.







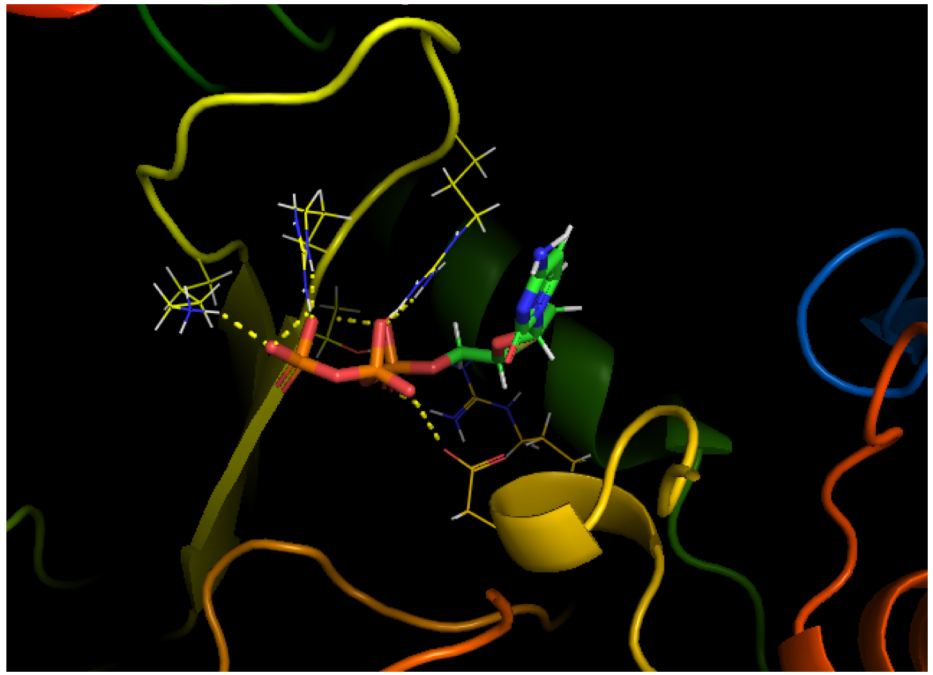


Figure 3. PLANTS in silico docking images for tenofovir diphosphate (top left), emtricitabine triphosphate (top right), abacavir triphosphate (bottom left) and lamivudine triphosphate (bottom right) against the RNA-dependent RNA Polymerase (RdRp) of SARS-CoV-2. Polar and Hydrogen interactions are represented by yellow dotted lines.

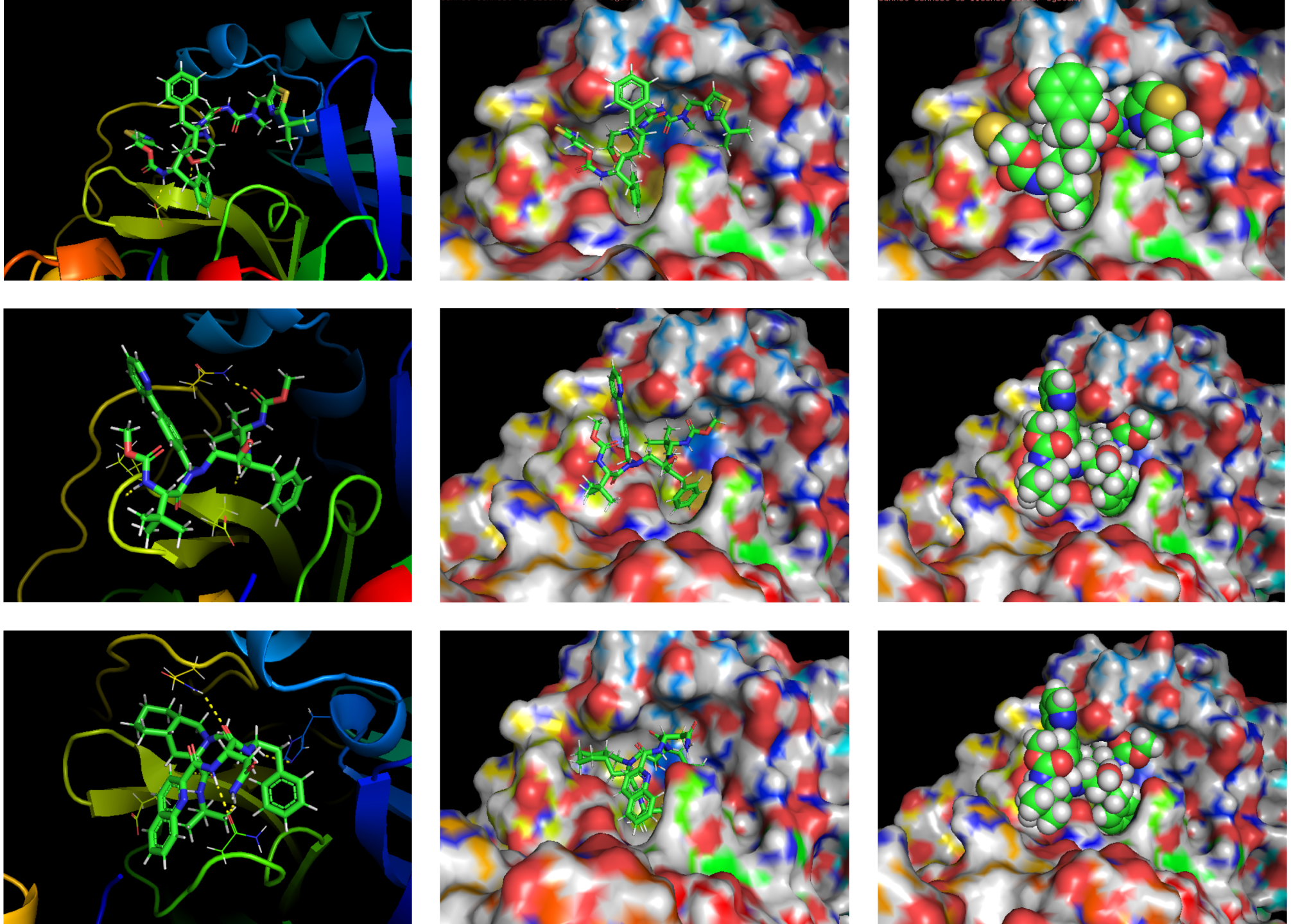


Figure 4. PLANTS in silico docking images for Cobicistat (top row), Atazanavir (middle row) and Saquinavir (bottom row) against the Main Protease (Mpro) of SARS-CoV-2. Polar and Hydrogen interactions are represented by yellow dotted lines.