TITLE: Search for SARS-CoV-2 inhibitors in currently approved drugs to tackle COVID-19 pandemia

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Different treatments are currently used for clinical management of SARS-CoV-2 infection, but little is known about their efficacy yet. Here we present ongoing results to compare currently available drugs for a variety of diseases to find out if they counteract SARS-CoV-2-induced cytopathic effect in vitro. Our goal is to prioritize antiviral activity to provide a solid evidence-driven rationale for forthcoming clinical trials. Since the most effective antiviral approaches are usually based on combined therapies that tackle the viral life cycle at different stages, we are also testing combinations of drugs that may be critical to reduce the emergence of resistant viruses. We will provide results as soon as they become available, so data should be interpreted with caution, clearly understanding the limitations of the in vitro model, that may not always reflect what could happen in vivo. Thus, our goal is to test the most active antivirals identified in adequate animal models infected with SARS-CoV-2, to add more information about possible in vivo efficacy. In turn, successful antivirals could be tested in clinical trials as treatments for infected patients, but also as pre-exposure prophylaxis to avoid novel infections until an effective and safe vaccine is developed.
INTRODUCTION

A novel betacoronavirus, the severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, is causing a large respiratory outbreak that began in Wuhan, China, in November 2019, and has now spread globally around the world (Chen et al., 2020). To date, there are no approved antiviral drugs for the specific treatment of human coronavirus infections. However, several drugs are being used in the frontline of clinical management of SARS-CoV-2-infected individuals in hospitals all around the world, to avoid the development of the Coronavirus Disease 2019 (COVID-19)-associated pneumonia, which can be fatal. Currently, different drug regimens are being applied, but no clinical study has evidenced their efficacy yet. Under this scenario, initiatives launched by the World Health Organization (WHO), such as the SOLIDARITY study that will compare Remdesivir, Hydroxychloroquine, Ritonavir/Lopinavir and Ritonavir/Lopinavir plus ß-interferon regimes, are of critical importance to prioritize the use of the most active compounds. As already envisioned in the SOLIDARITY trial, the most effective antiviral therapies are usually based on combined therapies that tackle distinct steps of the viral life cycle. These combinations may be critical to reduce the emergence of drug resistant viruses and to potentiate antiviral activity, enhancing their chances to improve clinical outcome.

We are currently testing the antiviral activity of different clinically available compounds and their combinations by assessing cellular cytotoxicity and viral induced cytopathic effect in vitro. By these means, we are calculating the concentration at which compounds and their combinations achieve a 50 % maximal inhibitory capacity (IC₅₀). This is an ongoing study that aims to compare currently available drugs and their possible combinations to counteract SARS-CoV-2-induced cytopathic effect in vitro, prioritizing their activity and providing a solid evidence-driven rationale to inform prospective clinical trials. Our strategy is circumscribed to compounds already approved for clinical use, since they are ideal candidates for entering into fast track clinical trials. Drug selection criteria has been first focused on compounds being currently tested in clinical trials, along with well-known HIV-1 and HCV protease inhibitors, as well as other inhibitors that have been suggested to have potential activity against SARS-CoV-2. Ongoing molecular docking studies are also being performed, and will inform about other possible candidates that could be repurposed for blocking SARS-CoV-2 replication.
Here we present results of our experiments while they are ongoing, so data should be carefully interpreted until sufficient replication studies that are underway become available. Yet, given the urgent situation we are facing and the fact that all the compounds we tested are already clinically approved, we report our ongoing experiments in the most expedited manner for the scientific community, clearly stressing the limitations of these preliminary data. In addition, it is also important to highlight that in vitro efficacy does not always translate into clinical efficacy, so even if replication studies confirm the results we are obtaining, well-designed and controlled clinical trials are needed to assess safety, efficacy and tolerability of any antiviral treatment or combination described herein. Assessing antiviral activity and safety in relevant animal models could be key to identify and advance those compounds with the highest potential to succeed in clinical trials. Thus, this project will produce a list of effective compounds with proven antiviral efficacy in vitro to halt SARS-CoV-2 replication, focusing on those that are already clinically approved for humans. In turn, this information could guide future clinical trials and offer a potential therapeutic benefit to individuals infected with SARS-CoV-2.

RESULTS

1. Antiviral activity of compounds that potentially inhibit viral entry
SARS-CoV-2 entry requires viral binding and spike protein activation via interaction with the cellular receptor ACE2 and cellular protease TMPRSS2 (Hoffmann et al., 2020), a mechanism favored by viral internalization via endocytosis. Interference with either of these initial processes has proven to decrease SARS-CoV-2 entry and infectivity (Hoffmann et al., 2020; Monteil et al., 2020). In addition, once SARS-CoV-2 accumulates in endosomes, cellular cathepsins can also prime viral Spike protein cleavage and favor viral fusion. Hence, we first tested compounds that could have an effect before viral entry by impairing viral-cell fusion (Table 1). Given its wide clinical use worldwide, we first confirmed the inhibitory effect of hydroxychloroquine (Dolquine®) on SARS-CoV-2 induced cellular cytotoxicity (Liu et al., 2020). A constant concentration of a SARS-CoV-2 stock sequenced upon isolation (accession ID EPI_ISL_418268 at GISAID repository: http://gisaid.org) was mixed with decreasing concentrations of hydroxychloroquine and added to Vero E6 cells. To control for drug-induced cytotoxicity, Vero E6 were also cultured with decreasing concentrations of
hydroxychloroquine in the absence of SARS-CoV-2. As shown in Fig. 1A, this drug was able to inhibit viral-induced cytopathic effects (red lines) at concentrations where no cytotoxic effects of the drug were observed (grey lines). The mean concentration of this drug that inhibited cytotoxicity at 50% (mean IC$_{50}$ value) was 1.27 ± 0.7 µM. These results aligned with previous reports highlighting the in vitro inhibitory capacity of chloroquine derivatives (Liu et al., 2020; Wang et al., 2020) and their preliminary benefit observed in a very small cohort of patients (Gautret et al., 2020) that should be confirmed in the ongoing large-scale randomized SOLIDARITY trial. Since hydroxychloroquine is being administered in combination with the antibiotic azithromycin (Gautret et al., 2020), which induces anti-viral responses in bronchial epithelial cells (Gielen et al., 2010), we further tested the activity of this compound (Zytromax®) in our assay. However, in the Vero E6 model, azithromycin did not show any antiviral effect (Fig. 1B), and the combination of hydroxychloroquine with azithromycin had a similar activity as the chloroquine derivative alone (Fig. 1C).

Additional FDA-approved compounds previously used to abrogate viral entry via clathrin-mediated endocytosis were also tested in this SARS-CoV-2-induced cytotoxicity assay (Table 1). Indeed, clathrin-mediated endocytosis is one of the potential mechanisms by which hydroxychloroquine may exert its therapeutic effect against SARS-CoV-2 (Hu et al., 2020). One of these compounds was Amantadine, licensed against influenza A virus infections and as a treatment for Parkinson's disease, which blocks coated pit invagination at the plasma membrane (Phonphok and Rosenthal, 1991). In addition, we also tested Chlorpromazine, an antipsychotic drug that inhibits clathrin-mediated endocytosis by preventing the assembly and disassembly of clathrin networks on cellular membranes or endosomes (Wang et al., 1993). When we assessed the antiviral efficacy of these clathrin inhibitors against SARS-CoV-2, we did not find any prominent effect, only a partial inhibition at 100 µM for Amantadine (Supp. Fig. 1). The broad cathepsin B/L inhibitor E64-d, which exerts activity against viruses cleaved by cellular cathepsins upon endosomal internalization, as is the case of Ebola virus (Gielen et al., 2010), showed also partial inhibitory activity (Supp. Fig. 1) as already described for pseudotyped SARS-CoV-2 viruses (Hoffmann et al., 2020). While these results could not be confirmed using the specific cathepsin B inhibitor CA-074-Me due to drug-associated toxicity, it is important to highlight that none of these cathepsin inhibitors is approved for clinical use. These data suggest that SARS-CoV-2
entry partially relies on clathrin-mediated endocytosis and cellular cathepsins that cleave the viral Spike protein allowing for viral fusion once SARS-CoV-2 is internalized in endosomes. However, as hydroxychloroquine activity was much more potent than that exerted by Amantadine or E64-d, it will be paramount to dissect other possible pathways that could be responsible for the potent antiviral effect of hydroxychloroquine (Fantini et al., 2020).

2. Antiviral activity of compounds that potentially inhibit post-viral entry steps.

Upon viral internalization, SARS-CoV-2 fuses with endosomal membranes and triggers viral RNA release into the cytoplasm, where polyproteins are translated and cleaved by proteases (Song et al., 2019). This leads to the formation of an RNA replicase-transcriptase complex that drives the production of negative-stranded RNA via both replication and transcription (Song et al., 2019). Negative-stranded RNA drives transcription of positive RNA genomes and translation of viral nucleoproteins, which assemble in viral capsids at the cytoplasm (Song et al., 2019). These capsids then bud into the lumen of ER-Golgi compartments, where viruses are finally released to the extracellular space by exocytosis. Potentially, any of these steps of the viral cycle is susceptible to be targeted with different antiviral compounds.

In our search for these antivirals, we first focused on Remdesivir, which has in vitro activity against SARS-CoV-2 after viral entry (Wang et al., 2020). Remdesivir is a broad-spectrum promising antiviral drug against Ebola virus (Mulangu et al., 2019) and other highly pathogenic coronaviruses such as SARS-CoV and MERS-CoV (Sheahan et al., 2017). Remdesivir acts as an adenosine analogue that is incorporated into nascent viral RNA chains and results in premature termination (Warren et al., 2016). Given its clinical safety proven during the last Ebola outbreak, Remdesivir is actually being assayed at the SOLIDARITY trial, and has shown efficacy in non-human primate animal models (Williamson et al., 2020). Here we further confirmed its in vitro capacity to inhibit SARS-CoV-2-induced cytotoxicity at concentrations where no cytotoxic effects of the drug were observed (Fig. 2A). The mean IC50 value of this drug was 0.85 ± 0.41 µM. In combination with hydroxychloroquine, however, Remdesivir did not improve its own antiviral effect when added alone (Fig. 2A). Yet, both hydroxychloroquine and Remdesivir showed the best IC50 values of all the compounds tested in this screening (Fig. 2B).
We also assessed other clinically approved protease inhibitors with potent activity against HIV-1. However, none of the HIV-1 protease inhibitors detailed in Table 1 showed remarkable protective cytotoxic activity against SARS-CoV-2 infection on Vero E6 cells. Lopinavir and Tipranavir inhibited cytotoxicity at the non-toxic concentration of 20 μM, and Amprenavir exhibited activity at the non-toxic concentration of 100 μM (Supp. Fig. 2). Darunavir, which is currently being tested in ongoing clinical trials, showed partial inhibitory activity at 100 μM, although this concentration had 8.5 ± 6.2 % of cytotoxicity associated (Supp. Fig. 2). Of note, other HIV-1 reverse transcriptase inhibitors such as Tenofovir, Emtricitabine and their combination also failed to show any antiviral effect against SARS-CoV-2 (Supp. Fig. 3). These results indicate that future clinical trials should address the value of including these anti-HIV-1 inhibitors considering the limited antiviral effect shown against SARS-CoV-2.

We also assessed the inhibitory capacity of HCV protease inhibitors, broad antivirals, anti-parasitic, anti-malarial, anti-influenza, and antifungal compounds (Table 1). Among these, only Favipiravir showed partial inhibitory activity at the non-toxic concentration of 100 μM.
DISCUSSION

We are currently assessing the antiviral activity of clinically approved compounds that may exert their antiviral effect alone or in combination. Combination therapies could provide a better antiviral potency while reducing viral resistance appearance. So far, we have tested more than 25 compounds and their combinations, and confirmed the effect of hydroxychloroquine and Remdesivir, the most potent antivirals of this screening, that did not increase their potency in combination. Remdesivir is not suitable for oral delivery as its poor hepatic stability would likely result in almost complete first-pass clearance (EMA, 2020), and therefore requires intravenous injection that complicates its use. Hydroxychloroquine, on the other hand, is orally available and has been shown to generate serum levels of 1.4 -1.5 μM at safe dosages in humans (Liu et al., 2020). While the mechanism of action of Remdesivir is clear, future work should address how hydroxychloroquine is actually interfering with viral replication, as this information could be key for identifying new prophylactic and therapeutic candidates (Hu et al., 2020). Other antivirals identified herein with very limited potency against SARS-CoV-2 cytopathic effect were Lopinavir and Tipranavir, although it is worth mentioning that the inhibiting 20 μM concentration identified is reachable in human plasma (Walmsley et al., 2008). These results warrant further assessment of other clinically available drugs that are necessary to increase our current arsenal against SARS-CoV-2 infection.

As this is an ongoing study that continuously provides results as soon as they become available, data presented herein should be interpreted with caution, clearly understanding the limitations of an in vitro model. Even if enough replication assays prove reproducibility, the IC₅₀ values of drugs obtained in vitro may not reflect what could happen in vivo upon SARS-CoV-2 infection. Thus, our next goal will be to confirm these data in adequate animal models as soon as enough potent candidates and their combinations are prioritized in this study. In turn, these results could provide a rational basis to perform future clinical trials not only for SARS-CoV-2 infected individuals, but also for pre-exposure prophylaxis strategies that could avoid novel infections. Prophylaxis could be envisioned at a population level or to protect the most vulnerable groups, and should be implemented until an effective vaccine is safely developed.
MATERIAL & METHODS

**Ethics statement.** The institutional review board on biomedical research from Hospital Germans Trias i Pujol (HUGTiP) approved this study. Individuals involved in this study gave their written informed consent to participate.

**Cell Cultures.** Vero E6 cells (ATCC CRL-1586) were cultured in Dulbecco’s modified Eagle medium, (DMEM; Lonza) supplemented with 5% fetal calf serum (FCS; EuroClone), 100 U/mL penicillin, 100 µg/mL streptomycin, and 2 mM glutamine (all ThermoFisher Scientific).

**Virus isolation, titration and sequencing.** SARS-CoV-2 virus was isolated from a nasopharyngeal swab collected from an 89-year-old male patient giving informed consent and treated with Betaferon and Dolquine for 2 days before sample collection. The swab was collected in 3 mL medium (Deltaswab VICUM®) to reduce viscosity and stored at -80ºC until use. Vero E6 cells were cultured on a cell culture flask (25 cm²) at 1.5 x 10⁶ cells overnight prior to inoculation with 1 mL of the processed sample, for 1 h at 37ºC and 5% CO₂. Afterwards, 4 mL of 2% FCS-supplemented DMEM were supplied and cells were incubated for 48 h. Supernatant was harvested, centrifuged at 200 x g for 10 min to remove cell debris and stored at -80ºC. Cells were assessed daily for cytopathic effect and the supernatant was subjected to viral RNA extraction and specific RT-qPCR using the SARS-CoV-2 UpE, RdRp and N assays (Corman et al., 2020).

Viral RNA was extracted directly from swab samples and from the isolate using the Nucleospin Virus kit (Macherey-Nagel, Duren, Germany) and transcribed to cDNA using the PrimeScript™ RT reagent Kit (Takara, Japan) using oligo-dT and random hexamers, according to the manufacturer's protocol. DNA was then processed with Nextera kit (Illumina) and loaded on Illumina 300bp paired-end sequencing with MiSeq Sequencing platform. Sequence reads were quality filtered and mapped against coronavirus reference (NC_045512.2) using bowtie2 tool (Langmead et al., 2012). Consensus genomic sequence was called from the resulting alignment at a 18x median coverage using samtools (Li et al., 2009). Genomic sequence was deposited at GISAID repository ([http://gisaid.org](http://gisaid.org)) with accession ID EPI-ISL_418268.
**Antivirals & compounds.** The complete list of compounds used for this study and vendors are shown in Table 1. Drugs were used at a concentration ranging from 100μM to 0.0512 nM at serial dilutions. When two drugs were combined, each one was added at a concentration ranging from 100μM to 0.0512 nM at serial dilutions.

**Antiviral activity.** Increasing concentrations of antiviral compounds were added to Vero E6 cells together with 10¹⁸ TCID₅₀/mL of SARS-CoV-2, a concentration that achieves a 50% of cytopathic effect. Non-exposed cells were used as negative controls of infection. In order to detect any drug-associated cytotoxic effect, Vero E6 cells were equally cultured in the presence of increasing drug concentrations, but in the absence of virus. Cytopathic or cytotoxic effects of the virus or drugs were measured at 3 days post infection, using the CellTiter-Glo luminescent cell viability assay (Promega). Luminescence was measured in a Fluoroskan Ascent FL luminometer (ThermoFisher Scientific).

**IC₅₀ calculation and statistical analysis.** Response curves of compounds or their mixes were adjusted to a non-linear fit regression model, calculated with a four-parameter logistic curve with variable slope. Cells not exposed to the virus were used as negative controls of infection and set as 100% of viability, and used to normalize data and calculate the percentage of cytopathic effect. All analyses and figures were generated with the GraphPad Prism v8.0b Software.
TABLES

Table 1. Antivirals tested in this study classified depending on their potential activity before or after viral entry. NA; Not active. TBD; To be determined.

FIGURES

Figure 1. Antiviral activity of hydroxychloroquine and azithromycin. Cytotoxic effect on Vero E6 cells exposed to a fixed concentration of SARS-CoV-2 in the presence of decreasing concentrations of hydroxychloroquine (Dolquine®), azithromycin (Zitromax®), and their combination. Drugs were used at a concentration ranging from 100 μM to 0.0512 nM. When combined, each drug was added at the same concentration. Non-linear fit to a variable response curve from one representative experiment with two replicates is shown (red lines), excluding data from drug concentrations with associated toxicity. IC50 value is indicated. Cytotoxic effect on Vero E6 cells exposed to decreasing concentrations of drugs in the absence of virus is also shown (grey lines).

Figure 2. Antiviral activity of Remdesivir alone or in combination with hydroxychloroquine. A. Cytotoxic effect on Vero E6 cells exposed to a fixed concentration of SARS-CoV-2 in the presence of decreasing concentrations of Remdesivir and its combination with hydroxychloroquine (Dolquine®). Drugs were used at a concentration ranging from 100μM to 0.0512 nM. When combined, each drug was added at the same concentration. Non-linear fit to a variable response curve from one representative experiment with two replicates is shown (red lines), excluding data from drug concentrations with associated toxicity. Cytotoxic effect on Vero E6 cells exposed to decreasing concentrations of drugs in the absence of virus is also shown (grey lines). B. IC50 values of Dolquine® and Remdesivir®. Data from two experiments including values obtained from three response curves including two replicates each.
SUPPLEMENTAL FIGURES

Supplemental Figure 1. Limited antiviral activity of entry inhibitors. Cytotoxic effect on Vero E6 cells exposed to a fixed concentration of SARS-CoV-2 in the presence of decreasing concentrations of Amantadine, a clathrin-mediated endocytosis inhibitor, or E64-d, a pan cathepsin inhibitor acting downstream once viruses are internalized in endosomes. Drugs were used at a concentration ranging from 100 μM to 0.0512 nM. Non-linear fit to a variable response curve from one experiment with two replicates is shown (red lines). Cytotoxic effect on Vero E6 cells exposed to decreasing concentrations of drugs in the absence of virus is also shown (grey lines).

Supplemental Figure 2. Limited antiviral activity of HIV-1 protease inhibitors. Cytotoxic effect on Vero E6 cells exposed to a fixed concentration of SARS-CoV-2 in the presence of decreasing concentrations of protease inhibitors against HIV-1. Drugs were used at a concentration ranging from 100 μM to 0.0512 nM. Non-linear fit to a variable response curve from one experiment with two replicates is shown (red lines), excluding data from drug concentrations with associated toxicity. Cytotoxic effect on Vero E6 cells exposed to decreasing concentrations of drugs in the absence of virus is also shown (grey lines).

Supplemental Figure 3. No antiviral activity of HIV-1 reverse transcriptase inhibitors. Cytotoxic effect on Vero E6 cells exposed to a fixed concentration of SARS-CoV-2 in the presence of decreasing concentrations of HIV-1 reverse transcriptase inhibitors. Drugs were used at a concentration ranging from 100 μM to 0.0512 nM. Non-linear fit to a variable response curve from one experiment with two replicates is shown (red lines). Cytotoxic effect on Vero E6 cells exposed to decreasing concentrations of drugs in the absence of virus is also shown (grey lines).
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COMPETING INTEREST
The authors declare that no competing financial interests exist.

AUTHOR CONTRIBUTION
Conceived and designed the experiments: JR, JS, BC, JVA, NIU
Performed the experiments: JR, MNJ, IE, JVA, NIU
Analyzed and interpreted the data: JR, MNJ, IE, AV, VG, JC, JB, JS, BC, JVA, NIU
Wrote the paper: JR, JVA, NIU

DATA AVAILABILITY
Data is available from corresponding authors upon reasonable request
| ACTIVITY | DRUG                                | IC<sub>50</sub> SARS-CoV-2 (Mean +/-SD) | Mode of Action                              | Previous Clinical Use    | Vendor Origen |
|----------|------------------------------------|--------------------------------------|-----------------------------------------------|--------------------------|--------------|
| ENTRY    | Hydroxichloroquine (Dolquine)      | 1.27 +/- 0.7 µM                       | Clathrin-mediated endocytosis or pH-dependent viral fusion inhibitor | Malaria                  | Laboratorios Rubio |
|          | Amantadine                          | Not calculated, but partially active at 100 µM | Clathrin-mediated endocytosis inhibitor       | Parkinson & influenza A  | Sigma Aldrich |
|          | Chlorpromazine (Largactil)          | NA                                   | Clathrin-mediated endocytosis inhibitor       | Antipsychotic            |              |
|          | CA-074-Me                           | NA                                   | Cathepsin inhibitor B                         | Not approved             | Sigma Aldrich |
|          | E-64d                               | 4287                                 | Cathepsin inhibitor B/L                       | Not approved             | Sigma Aldrich |
| POST-ENTRY| Remdesivir                          | 0.85 +/- 0.41 µM                     | Polymerase inhibitor                          | Ebola Virus              | Cayman Chemical |
|          | Saquinavir                          | NA                                   | Protease inhibitor                            | HIV-1                    | Reference standard HPLC |
|          | Lopinavir                           | Not calculated, but active at 20 µM  | Protease inhibitor                            | HIV-1                    | Abbot |
|          | Ritonavir                           | NA                                   | Protease inhibitor                            | HIV-1                    | Abbot |
|          | Tipranavir                          | Not calculated, but active at 20 µM  | Protease inhibitor                            | HIV-1                    | Reference standard HPLC |
|          | Nelfinavir Mesylate                 | NA                                   | Protease inhibitor                            | HIV-1                    | Roche Diagnostics |
|          | Amprenavir                          | Not calculated, but active at 100 µM | Protease inhibitor                            | HIV-1                    | GSK |
|          | Fosamprenavir Calcium               | NA                                   | Protease inhibitor                            | HIV-1                    | Sigma Aldrich |
|          | Darunavir                           | Not calculated, but partially active at 100 µM | Protease inhibitor | HIV-1 | Sigma Aldrich |
|          | Tenofovir                           | NA                                   | Reverse Transcriptase inhibitor               | HIV-1                    | Selleckchem |
|          | Emtricitabin (Emtriva)              | NA                                   | Reverse Transcriptase inhibitor               | HIV-1                    | Gilead |
|          | Velpatasvir                         | NA                                   | Protease inhibitor                            | HCV                      | Selleckchem |
|          | Sofosbuvir                          | NA                                   | Protease inhibitor                            | HCV                      | Selleckchem |
|          | Boceprevir                          | NA                                   | Protease inhibitor                            | HCV                      | Quimigen |
|          | Favipiravir                         | Not calculated, but partially active at 100 µM | RNA polimerase inhibitor | Flavivirus, Arenavirus, Bunyavirus, Alphavirus | Quimigen |
| UNKNOWN  | Azithromycin (Zitromax)             | NA                                   | Antibiotic                                   | Bacteria                 | Pfizer |
|          | Quinacrine dihydrochloride          | NA                                   | Inhibitor of NF-kappaB                       | Parasites                | Sigma Aldrich |
|          | Mefloquine hydrochloride            | NA                                   | Phospholipid bilayer?                        | Malaria                  | Sigma Aldrich |
|          | N-Acetil cystein (Flumil)           | NA                                   | Synthesis of glutathione                     | Influenza                |               |
|          | Itraconazole                        | TBD; Toxicity associated             | Inhibits OSBP, which produces the membrane-bound viral replication organelles | Fungus                   | Sigma Aldrich |
|          | Ivermectin (Stromectol)            | NA                                   | Nuclear import inhibitor                     | Parasites                |               |

Table 1
Dolquine

$IC_{50} = 2.076 \mu M$

Zitromax

$IC_{50} = \sim 0 \mu M$

Dolquine & Zitromax

$IC_{50} = \sim 1.126 \mu M$

Figure 1
Remdesivir

IC$_{50}$ = 1.169 μM

Remdesivir & Dolquine

IC$_{50}$ = 1.163 μM

Figure 2