

DRUGBANK WHITE PAPER

# COVID-19: Finding the Right Fit

Identifying Potential Treatments  
Using a Data-Driven Approach

## Update: March 26, 2020

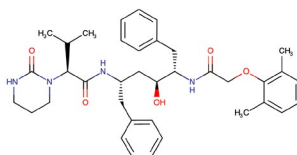
With the implications and research of COVID-19 quickly evolving, the DrugBank team has issued an addendum to the previously published report to provide updates and additional details about the outbreak.

### UPDATE SUMMARY

- The total number of confirmed global COVID-19 cases as of March 26 2020 is 523,163 with 23,639 deaths and a total of 122,059 recovered cases. These numbers will continue to change with ongoing infection and recovery.[1]
- The virus has spread to almost all countries worldwide, with a sharp decline in new cases diagnosed in South Korea.[1]
- In Wuhan, the initial epicenter of SARS-CoV-2, no new cases were reported on March 19th, suggesting widespread control of the infection and the possibility of ending containment measures. More recently, however, asymptomatic cases have been reported in this region.[2]
- COVID-19 continues to be a serious pandemic exerting significant downstream health and economic effects. The increase in demand for testing, medical equipment, and availability of the healthcare workforce has placed significant strain on most countries.
- A report by the CDC states that approximately 20% of patients hospitalized with COVID-19 in the US are aged 20-44. Patients aged 65 and above continue to suffer from an increased morbidity and mortality rate from COVID-19, particularly those with underlying medical conditions. [3]
- Social distancing measures have been adopted and legislated in various jurisdictions worldwide to slow the spread of SARS-CoV-2, with the goal of allowing healthcare systems to adapt and respond to this evolving pandemic.

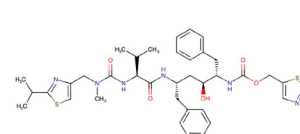
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### Lopinavir



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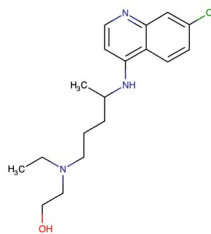
### Ritonavir



An open-label randomized control trial, conducted in the Hubei province of China between January 18th and February 3rd, recruited 199 patients hospitalized with COVID-19 to assess the benefit of lopinavir/ritonavir.[4] The combination failed to provide any benefit over standard therapy. While lopinavir/ritonavir does not appear to be an effective therapy for the treatment of COVID-19, the efficacy of this dual therapy in combination with other antiviral agents requires further investigation.

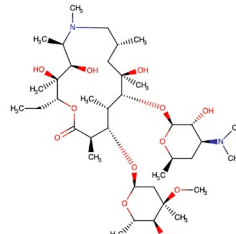
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### Hydroxychloroquine



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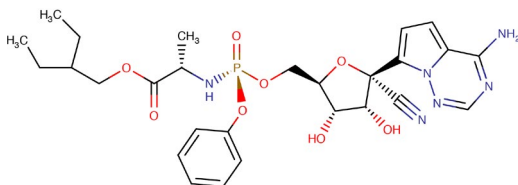
### Azithromycin



A recent open-label non-randomized study of hydroxychloroquine and azithromycin for the treatment of COVID-19 is gaining attention in the media.[5] This paper shows promising molecular results, significantly decreasing viral load in infected patients. However, clinical outcomes were not a measure of success and 1 patient in the treatment arm died, despite having a viral load of 0 the previous day. While these results form important preliminary results, further research must be performed before this treatment could be used outside of specialist care.

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## Remdesivir



While remdesivir is transitioning to larger scale clinical trials, it is closed to new compassionate use requests.[6] Phase III clinical trials are still ongoing.[7]

## Vaccines Update

The quest for a vaccine against COVID-19 continues to be challenging since there is much to be learned about the virus' properties, virulence, and how the human immune system responds to the virus.[8]

In order to produce an effective vaccine, many scientists have looked to vaccine development research conducted for similar viruses such as SARS-CoV and MERS-CoV.[9] Several vaccine platforms and target antigens have been explored to prevent these viruses, each with their pros and cons.[9] For example, a DNA-based vaccination in phase I and II clinical trials utilizes full-length spike, or S1, proteins as target antigens and is able to promote both T- and B-cell responses.[9,10] This type of information will continue to be valuable for scientists engaged in COVID-19 vaccine development.

The prospective COVID-19 vaccine manufactured by Moderna (mRNA-1273) is an mRNA vaccine encoding a modified SARS-CoV-2 prefusion stabilized spike protein.[11] The vaccine, which utilizes a lipid nanoparticle delivery system, was first injected into healthy adult volunteers in a phase I clinical study in the US on March 16. [9,11,12] In this trial, each subject received two doses of the vaccine 28 days apart.[13] While initial results from this trial may remain undetermined for months, health officials suspect the delivery of a vaccine to the general public will take at least one year.[13]

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The effects of COVID-19 have reverberated across the globe since late 2019, and have resulted in an influx of new research and data being produced on potential novel candidates to treat the virus. There is a vast amount of research that uses data-driven approaches to identify potential therapies for the virus, and much of the research that has been done has used data from resources like DrugBank. This paper will give an overview of COVID-19, ongoing research, and how data-driven drug repurposing using data from DrugBank is giving life to high-potential investigative treatments for this worldwide outbreak.

### COVID-19 OUTBREAK SUMMARY

Coronavirus disease 2019 (named COVID-19 on February 11, 2020 by the World Health Organization (WHO) [3,6]) was first identified in Wuhan, China near the end of 2019 [3]. It is caused by the virus known as SARS-CoV-2 (previously called 2019-nCoV). This name was chosen because the virus is related to the coronavirus that caused the SARS outbreak of 2003. The two viruses are different despite their genetic similarity [2]. COVID-19 is believed to be less lethal but much more infectious than SARS-CoV [4]. Until the recent outbreak, this virus had not been identified in humans [8].

The first death from COVID-19 occurred in a 61 year old male who had purchased goods from a seafood market in Wuhan. Several other cases of the disease were diagnosed and traced back to the seafood market at the end of 2019 and beginning of 2020 [7,9].

On January 30, 2020, the WHO identified the spread of SARS-CoV-2 to be a *Public Health Emergency of International Concern*. By this time, the virus had spread to all 31 provinces in China, with about 7700 cases reported across China and a death toll of 170. The outbreak has rapidly progressed, spreading to 75 countries worldwide, with cases identified in Asia, Europe, North and South America, Australia, and Africa.

As of March 4, 2020, the total number of confirmed cases of COVID-19 has risen to 95,075 with 3,252 total deaths and 51,156 recovered cases [5]. These numbers are subject to change with ongoing infection and recovery from COVID-19.

**Influenza (i.e. the flu) is more infectious than SARS-CoV-2, but the reported mortality rate of COVID-19 is about 3.4%, which exceeds the standard 1% mortality rate of the flu [10].**

### CLARIFICATION:

**SARS-CoV-2, previously called 2019-nCoV, is the causative virus of coronavirus disease (COVID-19) [1]**

### ABBREVIATIONS

**ACE2:** Angiotensin Converting Enzyme 2

**β-CoV:** Betacoronavirus

**COVID-19:** Coronavirus Disease

**HIV:** Human Immunodeficiency Virus

**MERS:** Middle East Respiratory Syndrome

**MERS-CoV:** Middle East Respiratory Syndrome Coronavirus

**RNA:** Ribonucleic Acid

**SARS:** Severe Acute Respiratory Syndrome

**SARS-CoV:** Severe Acute Respiratory Syndrome Coronavirus

**SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2

**2019-nCoV:** 2019 Novel Coronavirus

About 80% of those infected with SARS-CoV-2 are expected to recover without hospitalization [4]. The risk of serious illness resulting from SARS-CoV-2 is increased in elderly patients with pre-existing conditions, such as heart failure and diabetes [4]. Because this virus has not been previously identified in humans, research into prevention and treatment of COVID-19 is underway [10].

### WHAT IS SARS-COV-2?

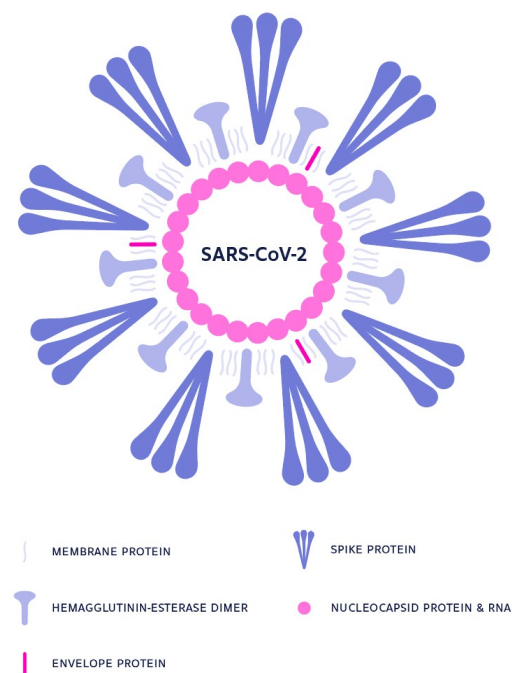
SARS-CoV-2 is an enveloped RNA virus belonging to the genus betacoronavirus (β-CoV). Other notable members of this genus include SARS-CoV and MERS-CoV [11,12]. The spike (S) protein of SARS-CoV-2 forms a trimer which then attaches to angiotensin converting enzyme 2 (ACE2) in the epithelial cells of the lungs, kidney, and small intestine; endothelial cells of the veins and arteries; and arterial smooth muscle cells [12,13].



The virus is spread through respiratory droplets from coughs and sneezes within approximately 6 feet or 1.8 metres and also by viral particles resting on surfaces [16,17]. SARS-CoV-2 is not expected to be an airborne virus [17].

The average incubation period of COVID-19 is 5.2 days [14]. After incubation, patients generally present with pneumonia, fever, cough, myalgia, dyspnea, and fatigue [15]. Less commonly, they may develop headache, hemoptysis, and diarrhea [15]. During an infection, there is an increase in pro-inflammatory cytokines such as interleukin-2, interleukin-7, interleukin-10, granulocyte colony-stimulating factor, interferon  $\gamma$ -induced protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 $\alpha$ , and tumor necrosis factor- $\alpha$  which may promote disease severity [15].

Chinese researchers recently discovered that SARS-CoV-2 had diverged into 2 strains, L-type and S-type, though information surrounding this mutation is controversial in the literature. The L-type strain of the virus is not only more transmissible than the S-type, but also the more predominant of the two [18]. It accounts for about 70% of cases and may impact the development of vaccines and therapies for COVID-19 [18].



## How Researchers Use DrugBank To Find Antiviral Candidates

In exploring novel therapies for COVID-19 researchers are leveraging artificial intelligence to aid in the discovery of potential candidates. Many are working in the drug repurposing space, using data from DrugBank and other data sources to narrow their funnel of potential treatments.

Drug repurposing (also commonly referred to as drug repositioning) is a drug development strategy used to identify novel uses for existing approved and investigational drugs outside of their original indication. This strategy offers numerous advantages over traditional drug development pipelines. Unlike traditional drug development, which risks failure in preclinical or early-stage clinical trials due to safety concerns, the process of drug repurposing mitigates this risk by utilizing drugs that have demonstrated safety records from previous trials. Drug repurposing is also significantly more efficient and cost effective than traditional drug development since pre-clinical and early-stage clinical trials do not need to be repeated[19].

In the past, drug repurposing often occurred serendipitously due to observed off-target (or previously unknown on-target) effects. For example, sildenafil is a phosphodiesterase

inhibitor that helps dilate blood vessels which was originally investigated for use as a cardiac agent in the treatment of angina pectoris. Patients in clinical trials noted a significant incidence of unwanted erections, and in 1996 sildenafil was patented and marketed instead for the treatment of erectile dysfunction under its now familiar alias: Viagra [20,21].

With the advances in artificial intelligence and machine learning, drug repurposing has shifted from being something serendipitous to a technologically-focused data-driven practice enhanced by comprehensive drug and chemical databases, including DrugBank.

Using structured data from DrugBank, researchers looking to find novel therapies for COVID-19 can incorporate AI methods, such as deep learning, into their drug repurposing research. More specifically, they can incorporate input data like crystal structures, and homology models of proteins and co-crystallized ligand fragments in order to predict the structures of drugs that will act as targets to these proteins.

Machine learning models learn the latent representations of structures to generate structures of antiviral drugs. Insilico Medicine's generative chemistry platform provides a comprehensive set of AI tools for training machine learning models on protein structure data in order to generate relevant antiviral structures. Protein structure data can be represented in the form of sequences (string) representations, graph representations, or in 3D spaces. Natural language processing (NLP), graph embedding, and computer vision can be used to train models to learn protein structures based on these representations respectively.

By leveraging machine learning techniques, researchers looking for novel therapies can be confident that drug repurposing efforts will be significantly more efficient, reducing the time and cost burden on researchers. By combining AI/ML and DrugBank's structured data, researchers can quickly navigate potential novel candidates, use data-driven decision making to narrow their research, and more efficiently find effective treatments for viruses like SARS-CoV-2 [25].

There are a number of specific use cases and examples of current research in drug repurposing related to COVID-19 treatments. In all of the cases below, the research includes the use of DrugBank's data.

Nguyen, et al. author of Potentially highly potent drugs for 2019-nCoV, **developed a structural-based drug repositioning (SBDR) ML model to screen 1465 approved drugs from DrugBank.** They found that the 3CL protease was 96% similar between SARS-CoV and SARS-CoV-2, and with this knowledge constructed a 3D putative structure of the SARS-CoV-2 3CL protease to perform a drug-target binding assay using DrugBank's data [22].



Like Nguyen, et al., researcher, Long Chen, **determined eight credible open reading frames (ORFs) with high homology to SARS-CoV-2 by analyzing the coronavirus genome and calculating binding parameters using SeeSAR.** From there, they used DrugBank to screen against seven different drugs that were selected based on DrugBank's sequence search module [23].



Using SeeSAR along with drug information for 2525 FDA-approved drugs pulled from the DrugBank database, Arya, et al., conducted virtual *in silico* screening to **identify molecules with the ability to inhibit any SARS-CoV-2 proteins essential for the viral reproductive cycle** [24].



Another study looking at novel candidates for COVID-19, used **high-throughput computational screening of a library of 8,000 experimental and approved drugs and small molecules obtained from DrugBank** to identify four molecules with high binding capacity for SARS-CoV-2's main protease [25].



DrugBank's data was also used by Junmei Wang, and Hosseini and Amanlou, in two studies that conducted virtual screenings. Wang focused on **"two-step hierarchical virtual screenings to identify repurposing drugs targeting the [SARS-CoV-2] protease,"** and tested the SARS-CoV-2 crystal structure against a series of datasets including approved, investigational, and experimental drugs. Unlike Wang, Hosseini and Amanlou focused only on approved drugs, and conducted virtual screening on 1615 FDA-approved drugs pulled from DrugBank [26,27].



The final example of a research study using DrugBank's data is the Khan et al. study that **tested a library of 123 existing antivirals available on DrugBank against two potential SARS-CoV-2 target proteins** [28].



The examples above highlight the multitude of ways in which DrugBank's data is utilized to improve and optimize drug discovery and repurposing. Further, the cases illustrate how drug information datasets like DrugBank have been and continue to be an indispensable tool for these processes. Drug repurposing is one of the most efficient ways to effectively respond to urgent health threats like the SARS-CoV-2 outbreak - hence research into promising treatment candidates will likely continue to focus on this method.

## Promising Drug Treatments For COVID-19

Although there is no known cure for coronavirus, healthcare providers are attempting to repurpose antivirals approved to treat other viral infections such as influenza, HIV, and Ebola. Interestingly, oseltamivir (Tamiflu) has shown some promise in slowing down SARS-CoV-2 despite the fact that oseltamivir was designed to target enzymes specific to the influenza virus. Scientists are hopeful that an investigational drug with a broad antiviral spectrum called remdesivir (marketed by Gilead) will be effective against coronaviruses [34]. While it was tested against Zaire Ebolavirus with no success, remdesivir was effective in blocking the replication of various coronaviruses in *in vitro* studies and animal models [28]. Remdesivir is currently being studied in Phase III trials and has been used successfully in one US patient. Gilead is aiming to conduct a large-scale clinical study consisting of patients with COVID-19 residing in China and other countries [29]. Remdesivir is also being investigated in a U.S. clinical trial as a breakthrough experimental treatment for COVID-19.

A rapid advice guideline was developed in December 2019 to address the need for a structured approach to the management of SARS-CoV-2. Information from guidelines addressing the management of similar respiratory illnesses such as SARS and MERS, as well as guidelines from the World Health Organization and the National Health Commission of the People's Republic of China was used to create this guideline. At present time there is weak evidence for treatment with inhaled interferon- $\alpha$  and oral lopinavir/ritonavir (Kaletra). Kaletra is being explored as combination therapy with several other medications including ribavirin, which inhibits RNA synthesis; umifenovir, which inhibits membrane fusion; and certain reverse transcriptase inhibitors [36].

Given that SARS-CoV-2 is a single stranded RNA  $\beta$ -CoV, some scientists recommend focusing on treatments that will target enzymes and machinery directly involved in its replication. Although antiretrovirals (e.g. Kaletra) used to treat HIV have been used and are currently being investigated for the treatment of SARS-CoV-2, it should be noted that this particular virus does not rely on reverse transcriptase which is a key target for antiretrovirals [35].

Favipiravir, or favilavir, was the first antiviral approved by the National Medical Products Administration of China for the treatment of COVID-19 after it demonstrated efficacy and an acceptable tolerability profile in a clinical trial that consisted of 70 patients with the disease [33,41]. Although specific details regarding the clinical trial are not currently available, the antiviral is an accepted experimental treatment for COVID-19 in both Japan and China [30,31]. Marketing for the drug was approved in February 2020, and Zhejiang Hisun

Pharmaceutical Company has begun mass production of the drug in response to the SARS-CoV-2 outbreak [28,30].

Ritonavir is currently being investigated in clinical trials in combination with other drugs, including danoprevir, oseltamivir, umifenovir, and darunavir [31,32].

Chloroquine, an anti-malarial drug with anti-inflammatory properties, was authorized by China's National Health Commission for the treatment of pneumonia associated with COVID-19. It was effective against SARS-CoV-2 *in vitro* and showed moderate clinical efficacy in multiple clinical trials across China in patients with COVID-19 [31,32].

Other drugs currently being investigated in laboratory testing and clinical trials include darunavir (in combination with cobicistat), galidesvir, and pifrenidone [31,32].

## Vaccines Under Development For COVID-19

Like other communicable diseases, preventing COVID-19 is far more effective than delivering treatment after infection [36]. Since vaccines are a cornerstone of disease prevention, various pharmaceutical companies are actively collaborating to pioneer vaccines for the prevention of COVID-19. Moderna Therapeutics has developed mRNA-1273, a vaccine currently under investigation in Phase I clinical trials. Moderna is also partnering with the National Institutes of Health (NIH) on a study commencing this April to assess the safety of its novel vaccine.

INO-4800, an experimental vaccine being developed by Inovio Pharmaceuticals, is in the preclinical stages of investigation. Inovio is collaborating with Beijing Advaccine Biotechnology to launch trials shortly examining its effectiveness [34]. A third international company involved in the development of an experimental vaccine is CureVac. Headquartered in Germany, CureVac is working with The Coalition for Epidemic Preparedness Innovations to design a manufacturing technology for the rapid production of vaccines. GlaxoSmithKline and Clover Biopharmaceuticals, a company based in China, are working together to develop a viral protein based vaccine. It is expected to be studied in clinical trials following the current preclinical study phase [34].

Finally, Johnson & Johnson, Regeneron Pharmaceuticals, Sanofi, and Vir Biotechnology are also seeking to develop vaccines for the prevention of COVID-19 [33].

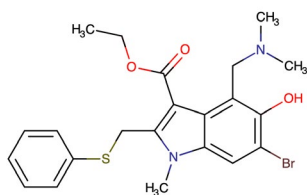
# Investigative Treatments

There are a number of high-potential investigative treatments for COVID-19 being explored. Below is an overview of the candidates being explored as treatments.

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## Umifenovir

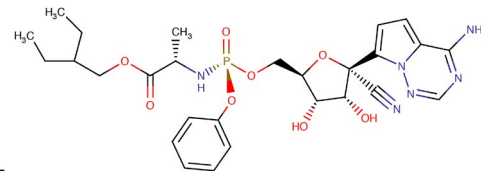
Umifenovir is an indole-based, hydrophobic, dual-acting direct antiviral/host-targeting agent used for the treatment and prophylaxis of influenza and other respiratory infections [49]. It has been in use in Russia for approximately 25 years and in China since 2006. Its invention is credited to a collaboration between Russian scientists from several research institutes 40-50 years ago, and reports of its chemical synthesis date back to 1993 [49]. Umifenovir's ability to exert antiviral effects through multiple pathways has resulted in considerable investigation into its use for a variety of enveloped and non-enveloped RNA and DNA viruses. This dual activity may also confer additional protection against viral resistance, as the development of resistance to umifenovir does not appear to be significant. Umifenovir is currently being investigated as a potential treatment and prophylactic agent for COVID-19 caused by SARS-CoV-2 infections in combination with both currently available and investigational antiviral therapies.



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## Remdesivir

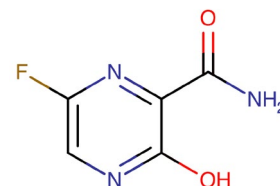
Remdesivir, or GS-5734, is an adenosine triphosphate analog first described in the literature in 2016 as a potential treatment for Ebola [39]. In 2017, its activity against the coronavirus family of viruses was also demonstrated [40]. Remdesivir is also being researched as a potential treatment for SARS-CoV-2, the coronavirus responsible for COVID-19 [40].



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## Favipiravir

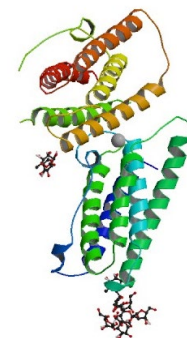
Favipiravir has been approved in Japan since March 2014 for the treatment of resistant cases of influenza, and has more recently gained traction in both Japan and China as an experimental treatment for SARS-CoV-2 [41]. In a clinical trial involving 70 patients, the antiviral demonstrated efficacy in treating SARS-CoV-2 and was well tolerated (more specific details regarding the clinical trial have not been released) [41,43]. Marketing for the drug was approved in February 2020, and Zhejiang Hisun Pharmaceutical Company has begun mass production of the drug in response to the SARS-CoV-2 outbreak [41,43].



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## Interferon Beta

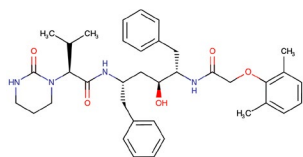
Interferon- $\beta$  is a cytokine disease-modifying agent initially approved to treat certain forms of Multiple Sclerosis (MS). Type 1  $\beta$ -interferons regulate the immune system, conferring protection against bacterial and viral replication. Interferon- $\beta$  was initially approved by the FDA in 1993. Some *in vitro* studies have determined that it can effectively clear other types of coronavirus, including SARS-CoV of 2003 and MERS-CoV of 2016 [44,45,46,47]. *In vivo* findings differ and report varying levels of success [46,50]. These findings may not translate to efficacy in the treatment of SARS-CoV-2 of 2019 in humans; however, genetic similarities between the viruses may be the basis for the development of future therapies. Human trials are not yet underway for treating SARS-CoV-2 with interferon- $\beta$ .





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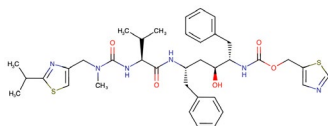
## Lopinavir



Lopinavir/ritonavir is a combination product marketed under the brand name Kaletra. It is an HIV-1 protease inhibitor that was first approved in the United States in 2000 for the treatment of HIV-1 infection, often in combination with other antiretrovirals. [36,53] Historically, low-level evidence has suggested that the combination provided benefit in the treatment of previous coronavirus outbreaks, such as SARS-CoV and MERS-CoV, and it may be particularly useful in the treatment of early SARS-CoV-2 infections [37].

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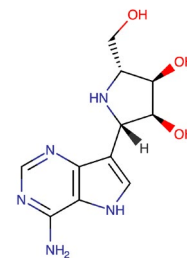
## Ritonavir



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## Galidesivir

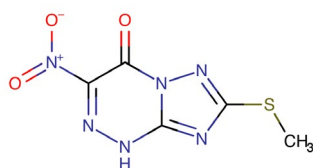
Galidesivir is an adenosine analogue that has been investigated for use against Zaire Ebolavirus [59]. *In vitro*, it displayed broad-spectrum antiviral activity against various negative- and positive-sense RNA viruses [60]. This drug has demonstrated antiviral action against other coronaviruses [33]. Phase 1 clinical trials have begun to determine the safety of this drug in humans [61]. Because of its activity against other coronaviruses, it may be studied as a potential therapy for COVID-19.



DB15622

## Triazavirin

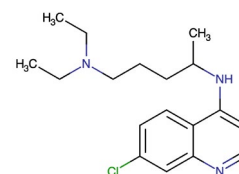
Triazavirin is an antiviral originally developed in Russia that has shown efficacy against influenza A and B, including the H5N1 strain [54,56]. It appears that triazavirin has shown promise in reducing influenza disease severity and associated complications [55]. Given the similarities between SARS-CoV-2 and H5N1, health officials are investigating triazavirin as an option to combat SARS-CoV-2 [56].



DB00608

## Chloroquine

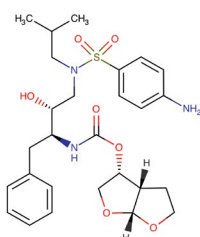
Chloroquine is currently undergoing clinical trials in China as a potential treatment for COVID-19 [59]. Chloroquine has been demonstrated to increase the pH of endosomes and inhibit glycosylation of ACE2, preventing viral entry into cells [58,59]. Studies *in vitro* have shown inhibition of infection at concentrations seen in patients taking chloroquine [58,59].



DB01264

## Darunavir

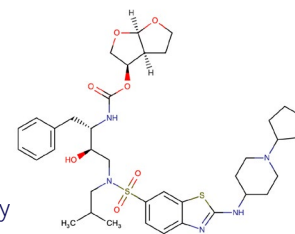
Darunavir is a protease inhibitor used with other HIV protease inhibitor drugs as well as ritonavir for the management of HIV-1 infection. As a second generation protease inhibitor, darunavir is designed to combat resistance to standard HIV therapy. It was initially approved by the FDA in 2006. Preliminary results from *in vitro* studies indicate that darunavir combined with umifenovir, an antiviral used to treat the flu in Russia and China, is effective in suppressing SARS-CoV-2 [49]. Another *in vitro* study also supports the use of darunavir in SARS-CoV-2 treatment [50]. Clinical trials in humans are underway that combine darunavir and cobicistat (a boosting agent), and are expected to conclude in August 2020 and determine the efficacy of this combination in clearing SARS-CoV-2 [52]. It is currently unclear whether the *in vitro* effects of darunavir combined with boosting agents will translate to clinical effects in humans [46], but clinical trials may provide further insight [35].



DB15623

## TMC-310911

TMC-310911 (also known as ASC-09) is a novel investigational protease inhibitor that is structurally similar to the currently available darunavir [62]. It has been investigated for use in HIV-1 infections. It may offer advantages over existing HIV therapies, such as a broader *in vitro* resistance profile as compared to other approved protease inhibitors [62].



# Staying up to date.

While this paper is not conclusive and research is ongoing, it provides evidence for the value of using data-driven approaches to find effective therapies for COVID-19. Ultimately, combining the power of artificial intelligence and machine learning tools with the structured data in Drugbank will allow researchers to more efficiently repurpose drugs for the treatment of this outbreak.

COVID-19 is still under investigation and there is no definitive solution to the outbreak at this time. The DrugBank database is updated regularly to reflect current research. Stay up to date regarding investigational treatments for COVID-19 by visiting [www.drugbank.ca](http://www.drugbank.ca).

## DISCLAIMERS:

1. This list of potential candidates is not exhaustive, and research in this area is constantly evolving.
2. This paper is not synonymous with medical advice. If you suspect you have COVID-19, please contact a medical professional.
3. Because of the COVID-19 outbreak, you should exercise frequent hand washing with soap and water, cover your mouth when you cough or sneeze, stay home if you feel ill, and avoid touching your face, eyes, and mouth.

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