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Synthetic small molecule based anti-viral chemical drugs as treatment options for COVID-19: New updates review

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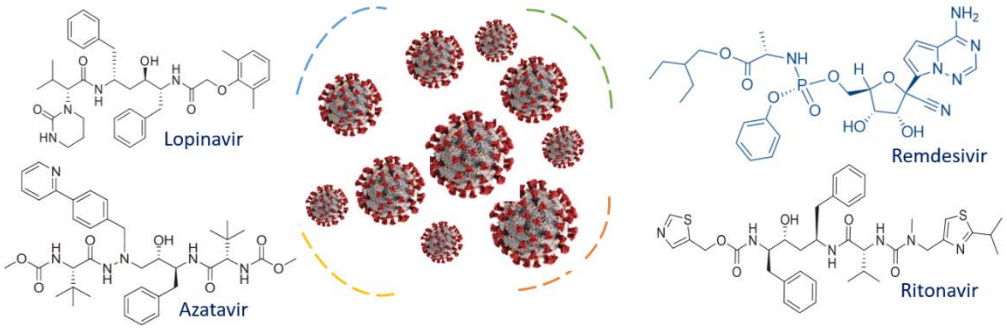
ABSTRACT



The SARS-CoV-2 outbreak and subsequent pandemic that began in late 2019 has presented a significant challenge to global health. Currently, numerous small-molecule therapeutic candidates are being evaluated in clinical setting for the inhibition of SARS-CoV-2 infection, and further alleviation of associated symptoms like cytokine storms and related complications. A diverse class of small molecules have been developed as anti-viral molecules. These molecules have anti-viral properties by action on different stage of life cycle of virus, like fusion inhibitors, reverse transcriptase inhibitor, integrase inhibitors, protease inhibitors, new virion formation inhibitors. On the analogy of action, these molecules are being proposed and tested for the SARS-CoV-2 infection. In this review, different existing anti-viral molecules that have promising activity for the treatment of Covid-19 have been discussed. This article provides a comprehensive overview of these small-molecule therapeutics, drawing on insights from medicinal chemistry research. It focuses on RNA-dependent RNA polymerase (RdRp) inhibitors, such as nucleoside analogues like remdesivir, favipiravir, and ribavirin. The discussion also delves in the clinical status of anti-viral drugs in treatment of Covid-19.

Keywords: COVID-19, SARS-CoV-2, Corona Virus, Nucleoside drugs, Smal-molecule drugs, Heterocyclic drugs.

INTRODUCTION

An outbreak of an infectious disease in China in December 2019 led to a significant number of deaths and the intermittent spread of the infection to other countries.[1] Those infected exhibited pneumonia symptoms, which progressed to Severe Acute Respiratory Syndrome (SARS). This viral infection proved to be lethal, causing numerous deaths due to respiratory complications. Initially reported in China, the virus quickly spread to nearly all other countries and continents, with a large number of confirmed cases in South Korea, Italy, Iran, as well as a few cases in South Africa, the USA, and other regions.[2] According to recent updates from the World Health Organization (WHO) and other monitoring institutions, the virus had infected more than 90,000 people worldwide, resulting in over 3,000 deaths by early 2020.[3] China, the hardest-hit country, recorded more than 2,500 deaths by the end of February 2020. The virus's sudden emergence and rapid transmission led to an epidemic situation. While the exact origin of the virus remains

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unconfirmed, it is speculated to have originated from animals consumed as food in China. Early transmission studies linked the initial infections to a local fish and wild animal market in China, suggesting the possibility of animal-to-human transmission. However, the virus later spread predominantly through human-to-human transmission. This disease proved to be highly lethal and bore a strong resemblance to Severe Acute Respiratory Syndrome (SARS).[3]

Recognizing the urgency and the need for a unique identification of the disease, the World Health Organization (WHO) officially named the epidemic disease caused by the novel coronavirus as "Coronavirus Disease 2019" (COVID-19) on February 11, 2020. The virus, belonging to the coronavirus family and first identified in 2019, was initially named "2019-nCoV." Later, based on an analysis of its evolutionary history and its similarities to the pathogen causing SARS, the virus was formally named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) by the International Committee on Taxonomy of Viruses on February 11, 2020.

The COVID-19 epidemic is part of a series of recent health emergencies caused by various pathogens.[4] The World Health Organization (WHO) has declared the COVID-19 outbreak as the sixth public health emergency of international concern, following previous emergencies such as H1N1 (2009),[5] polio (2014),[6] Ebola in West Africa (2014),[7] Zika (2016),[8] and Ebola in the Democratic Republic of Congo (2019).[9] The sudden emergence and rapid spread of this novel coronavirus in December 2019 have created an urgent need for developing methods for the quick diagnosis of the SARS-CoV-2 virus and the COVID-19 disease.

Doctors have been managing COVID-19 infections using a few existing drugs, with varying degrees of success reported. Researchers, backed by various international agencies and institutions, are deeply involved in understanding the mechanisms of infection, virulence, pharmacology, and the potential for early drug and vaccine development. This review covers the latest advancements in therapeutic development, as well as the potential of existing antiviral drugs.

COVID-19 TREATMENT REGIME

There is an urgent need for effective therapeutics to treat the newly emerged COVID-19. The severe nature of the infection has generated significant fear among patients[10] and the general public. COVID-19 is a novel respiratory disease (SARS) with a highly lethal potential, and while existing drugs have been somewhat effective in managing symptoms, no definitive treatment or therapeutic protocol has been established yet. To curb the spread of the virus, early prevention has been prioritized by nations worldwide. International organizations like the WHO have called for the rapid development of vaccines, drugs, and diagnostic tools for SARS-CoV-2 and COVID-19.

At a recent two-day international forum in Geneva, Switzerland, aimed at assessing the COVID-19 outbreak, WHO Director-General T.A. Ghebreyesus highlighted the need to develop candidate therapeutics and user-friendly diagnostics for detecting active, asymptomatic, and resolved COVID-19 infections. Understanding the virus's infection mechanism, particularly how it enters host cells and multiplies using the host's cellular machinery while causing cell damage, is crucial for therapeutic development.[11]

Given the limited knowledge about SARS-CoV-2, most of the drugs used so far to manage COVID-19 symptoms are based on treatments for similar past infections.[12] Treatment efforts have primarily focused on symptom management. Various antiviral drugs, either used for similar infections or chosen based on presumed mechanisms of SARS-CoV-2, are being considered for COVID-19 control.

Some potential drugs for immediate use or new therapeutic development include:

Entry Inhibitors: SARS-CoV-2 primarily infects the respiratory system, with the alveoli cells in the lungs being the target for infection. The virus generally enters host cells by forming a complex between its spike proteins[13] (the crown-like projections) and the receptors on the host cell.[14] Although the exact structure of the spike proteins and host cell receptors for SARS-CoV-2 is not fully understood, it is believed that the virus shares similarities with the earlier coronavirus (β-family) responsible for SARS.[11] Recent findings suggest that Angiotensin-Converting Enzyme 2 (ACE2) serves as the cellular receptor for both SARS-CoV and SARS-CoV-2. ACE2 shares some homology with Angiotensin-Converting Enzyme (ACE) but is not inhibited by ACE inhibitors.[15] In previous SARS cases, infections were initiated by the transmembrane spike (S) glycoprotein, which binds to host receptors and fuses the viral and cellular membranes. While identifying the exact structure of the viral spike proteins will take time, the development or screening of heterocyclic molecules as potential drugs may provide leads in creating effective entry inhibitors.[15]

Replication Inhibitors: Coronaviruses are RNA viruses that rely on the host cell's machinery to replicate their genome. The viral genome encodes a protein called RNA-dependent RNA polymerase (RdRp), which enables the transcription of the viral genome into new RNA copies.[16] This replication process is a key target for controlling viral infections. Nucleoside analogues, which are potential polymerase inhibitors used as antiviral drugs, could be effective against SARS-CoV-2.

SARS-CoV-2 is a positive-sense single-stranded RNA (ssRNA) virus that can infect humans. The virus primarily spreads from person to person through close contact and by inhaling droplets produced by sneezing or coughing. The 30-kilobase genome of SARS-CoV-2 includes 14 open reading frames (ORFs) that encode at least 27 proteins. At the 3′ end of the genome, four structural proteins-spike, envelope, membrane, and nucleocapsid-are encoded, along with eight accessory proteins that interfere with the host's innate immune responses. The ORF1ab region at the 5′ end encodes a polyprotein, which is cleaved into 16 nonstructural proteins (nsp 1-16) to form a replicase/transcriptase complex (RTC). The key enzyme within the RTC is RNA-dependent RNA polymerase (RdRp or nsp12). In RNA viruses like SARS-CoV-2, RdRp is essential for RNA synthesis, as well as for the coordinated replication and transcription of genomic RNA.[16]

Remdesivir, an RNA polymerase inhibitor that is a nucleotide adenosine analogue originally developed for Ebola and other RNA viruses, has shown promising results in controlling SARS-CoV-2 pneumonia in in vitro cell cultures and selected clinical cases. However, its application requires further evaluation with a larger patient population. Other nucleoside analogues, including DNA synthesis inhibitors like tenofovir disoproxil and lamivudine, along with similar antiviral agents,[17] have the potential to inhibit the replication of SARS-CoV-2. These are currently being assessed through molecular docking studies and laboratory tests on infected cell cultures.

REMDESIVIR

Remdesivir (Figure 1), developed by Gilead Sciences, is a broad-spectrum antiviral drug candidate currently in the research and development phase. Initially, its primary clinical application was intended for treating Ebola virus (EBOV) infections. However, due to its lackluster performance in a phase III clinical trial for Ebola virus disease (EVD), remdesivir has not received approval for sale in any country.

Despite this, remdesivir has shown activity against coronavirus pathogens like Middle East respiratory syndrome-related coronavirus (MERS-CoV)[18] and SARS-CoV, both of which share structural similarities with SARS-CoV-2.[19] This effectiveness has been observed in both in vitro and in vivo studies using animal models. Recent in vitro research suggests that remdesivir is also effective against SARS-CoV-2. Specifically, the drug demonstrated promising results when administered to the first reported COVID-19 patient in the United States as an experimental treatment. Currently, several governments, NGOs, and regulatory bodies are using remdesivir as an emergency treatment for COVID-19 due to the lack of approved alternatives.[20] However, the limited data from compassionate use cases are insufficient to fully assess the drug's safety and efficacy, which necessitates further clinical trials.[21]

Several clinical trials investigating the use of remdesivir for treating COVID-19 have been registered on ClinicalTrials.gov. These trials aim to evaluate the drug's safety and efficacy in adults with COVID-19. Additionally, two expanded access studies have been initiated to establish a treatment protocol for COVID-19. These ongoing trials are expected to yield more definitive results within two months. Preliminary findings indicate that remdesivir shows efficacy in treating COVID-19.[22]

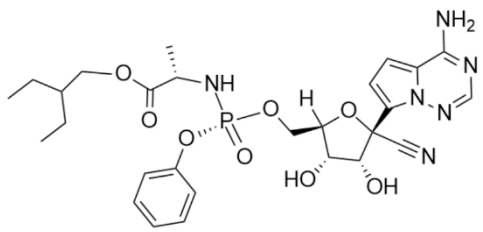

Figure 1. Chemical struture of Remdesivir

Remdesivir acts as an RdRP inhibitor, achieving its antiviral effects by blocking the synthesis of viral nucleic acids. SARS-CoV-2, an enveloped, positive-sense, single-stranded RNA virus, relies on RdRP—encoded by the virus itself—for its genomic replication. Once the virus enters the host cell, its genomic RNA serves as a template, utilizing the host cell's protein synthesis system to translate RdRP.[19] RdRP then plays a crucial role in synthesizing the negative-strand subgenomic RNA, producing mRNAs for various structural proteins, and replicating the viral genomic RNA. By accurately synthesizing tens of thousands of nucleotides, RdRP facilitates all the subsequent biological activities of the virus within the host cell. Given its central role, RdRP is a prime target for broad-spectrum antiviral drugs. Currently, most anti-coronavirus drugs targeting RdRP are either nucleoside (Nuc) analogs or RNA interferons.[23]

Remdesivir itself is a monophosphoramidate prodrug of an adenosine analog. Once inside the host cell, it undergoes conversion to nucleoside monophosphate (NMP), which is then further dephosphorylated into the active nucleoside triphosphate (NTP). NTP, structurally similar to adenosine triphosphate (ATP), competes for binding to the viral RdRP. Upon binding, NTP is incorporated into the RNA synthesis chain at a specific position, leading to RNA chain termination a few bases downstream from that position, typically at position i+5. This "chain termination" process effectively halts the replication of the virus.[23]

FAVIPIRAVIR

Favipiravir (also known as T-705)(Figure 2) is a broad-spectrum anti-RNA virus drug that was approved in 2014 for the oral treatment of influenza A and B infections. Research has shown that Favipiravir also exhibits strong antiviral effects against a variety of RNA viruses, including Ebola and rabies viruses, in addition to influenza.[24] Wang et al. demonstrated that Favipiravir can effectively reduce SARS-CoV-2 infection in vitro (EC50 = 61.88 μM, CC50 > 400 μM, SI > 6.46).[22]

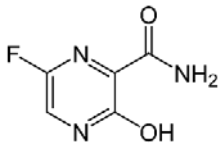

Figure 2. Chemical structure of Favipiravir

Ongoing clinical trials have indicated that Favipiravir can accelerate the recovery of COVID-19 patients, with a median recovery time of 2.5–9 days, compared to 11 days (8–13 days) for the control group.[25] Patients with non-severe COVID-19 treated with Favipiravir exhibited a shorter virus clearance time and showed significant improvement on chest CT scans. Additionally, patients in the Favipiravir group experienced fewer adverse reactions and better tolerance.[25]

A clinical trial conducted in Wuhan reported that among patients with common COVID-19, the 7-day clinical recovery rate for those treated with Favipiravir was 71.43%, significantly higher than the 55.68% recovery rate in the control group. Furthermore, Favipiravir treatment significantly shortened the time to fever and cough relief in patients with hypertension or

diabetes. Phase III clinical trials for the treatment of hospitalized patients with SARS-CoV-2 infection are ongoing, and future large-scale trials will be crucial in confirming the effectiveness and safety of Favipiravir as a COVID-19 treatment.[26]

Favipiravir is a newly discovered RNA-dependent RNA polymerase (RdRp) inhibitor, similar to Ribavirin. Beyond its anti-influenza properties, clinical experiments have demonstrated its ability to block the replication of various RNA viruses, including flaviviruses, alphaviruses, filoviruses, bunyaviruses, arenaviruses, noroviruses, and others. Once inside cells, Favipiravir is converted into an active phospho-ribosylated form (F-RTP), which is recognized by viral RNA polymerase as a substrate, thereby inhibiting the enzyme's activity.[26] This suggests that Favipiravir may have potential antiviral efficacy against SARS-CoV-2.[27] To explore this possibility, the Clinical Medical Research Centre of the National Infectious Diseases, in collaboration with the Third People's Hospital of Shenzhen, conducted a clinical trial on February 14, 2020, and obtained promising results. The preliminary findings indicated that the antiviral efficacy of Favipiravir surpasses that of the Lopinavir-ritonavir combination.[27]

RIBAVIRIN

Ribavirin (Figure 3), an FDA-approved synthetic guanosine analogue with antiviral properties, is often used in combination with other antiviral drugs, particularly interferon-alpha (IFN-a), to treat various viral infections, including chronic hepatitis C, viral hemorrhagic fevers, and respiratory syncytial virus (RSV) infections.[28] First commercialized in the early 1980s for treating RSV in children, Ribavirin has established itself as a standard antiviral agent, outperforming some newer drugs.[28]

Ribavirin is considered a broad-spectrum antiviral agent effective against both DNA and RNA viruses by inhibiting the production of viral messenger RNA through its interaction with RNA-dependent RNA polymerase (RdRp).[28] It is also a prodrug that metabolizes into nucleoside analogues, which block viral RNA synthesis and viral mRNA capping.[29] Ribavirin has shown effectiveness against diseases such as Crimean-Congo hemorrhagic fever, Hantavirus infection, Lassa fever, and Venezuelan hemorrhagic fever. Additionally, combining Ribavirin with Interferon-alpha has previously shown promise in treating MERS-CoV.[28]

However, conflicting results have been reported for MERS-CoV patients treated with Ribavirin[30] and two forms of interferon-alpha: IFN-a 2b and IFN-b1. One notable side effect of Ribavirin is its impact on hemoglobin levels in red blood cells, which is particularly problematic for patients with respiratory disorders, limiting its potential as a potent antiviral agent against coronavirus infections. Despite this, during the 2003 SARS-CoV outbreak, some countries, including China and Canada, successfully used high doses of Ribavirin in combination with antibiotics and hormones to combat the virus. Moreover, a combination of Ribavirin with lopinavir-ritonavir has shown potential against SARS-CoV-2.[28]

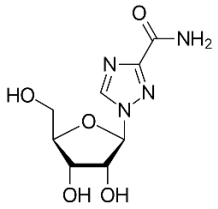

Figure 3. Chemical structure of Ribavirin

Ribavirin (ICN-1229) can induce antiviral activity against various RNA viruses by increasing the mutation rate in their genomes. It is primarily used to treat hepatitis C and viral hemorrhagic fevers.[29] Ribavirin also inhibits viral mRNA guanylyltransferase and mRNA 2′-O-methyltransferase in DENV and was used as a therapeutic during the SARS outbreak in 2003.[31,32] However, a comparison by Tong et al. of ribavirin and supportive therapies for severe COVID-19 patients showed that ribavirin did not significantly improve the time to negative conversion in SARS-CoV-2 tests or reduce mortality rates in severe cases.[33]

A clinical trial evaluated the safety and effectiveness of combining interferon beta-1b, lopinavir-ritonavir, and ribavirin for treating COVID-19. The study found that early triple antiviral therapy was safe and more effective than lopinavir-ritonavir alone in easing symptoms, shortening the duration of viral shedding, and reducing hospital stay for patients with mild symptoms, with mild and manageable side effects.[34] However, these findings need further validation through a larger double-blind trial. The safety of ribavirin remains controversial due to reported adverse effects, including teratogenicity and hemolytic anemia.[33,34]

LOPINAVIR

Lopinavir (Figure 4) is a medication typically used in combination with other antiviral drugs, such as ribavirin, to treat Human Immunodeficiency Virus (HIV). It belongs to a class of protease inhibitors that can target the non-structural protein 3CLpro of SARS-CoV. Research by Chu et al.[35] found that the combination therapy of lopinavir-ritonavir with ribavirin exhibited anti-SARS-CoV activity both in vitro and in clinical studies involving non-randomized trials.[36] Patients treated with this combination had a lower mortality rate compared to those in the control group, who received a combination of ribavirin and corticosteroids. When MERS-CoV emerged, further research identified lopinavir as effective against the virus in vitro.

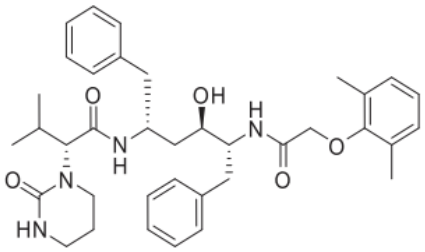

Figure 4. Chemical structure of Lopinavir

Although this drug combination can cause minor side effects, such as diarrhea, it has been recommended as an effective treatment for SARS-CoV-2 in China.[34,37] Ongoing investigations by Chinese researchers and clinicians continue to explore the therapeutic efficacy of the lopinavir-ritonavir combination.[36]

AZATAVIR

Atazanavir (figure 5) is an FDA-approved antiretroviral medication commonly used for the treatment and prevention of HIV.[38] It stands out among other protease inhibitors because it only requires a once-daily dosage, rather than multiple doses, and has a lesser impact on the patient's lipid profile. As an azapeptide HIV-1 protease inhibitor, Atazanavir works by binding to the protease active site, thereby inhibiting the enzyme's activity. Due to its antiviral properties, a deep learning model known as MT-DTI has demonstrated Atazanavir's inhibitory potency, with a Kd value of 94.94 nM against the SARS-CoV-2 3C-like protease.[39] This enzyme is also present in coronaviruses, where it plays a critical role in cleaving the coronavirus polyprotein at several conserved sites.[40]

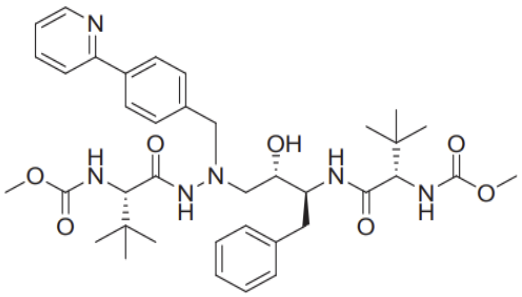

Figure 5. Chemical structure of Azatavir

RITONAVIR

Ritonavir (figure 6), an antiretroviral medication primarily used in the treatment of Human Immunodeficiency Virus (HIV), gained significant attention as a potential treatment for COVID-19.

Ritonavir is a protease inhibitor that was initially developed to inhibit the HIV-1 protease enzyme, which is crucial for the viral replication process. By binding to the active site of the protease enzyme, Ritonavir prevents the cleavage of viral polyproteins, thereby inhibiting the maturation of infectious viral particles. In the context of COVID-19, Ritonavir's mechanism was hypothesized to work similarly by inhibiting the SARS-CoV-2 main protease (Mpro, also known as 3CLpro), an enzyme critical for the replication of the coronavirus. By blocking this enzyme, Ritonavir could potentially reduce viral replication and, consequently, the severity of the infection.

Given its success in treating HIV, Ritonavir was repurposed for use against COVID-19, often in combination with other antiviral drugs, particularly Lopinavir. The combination of Lopinavir and Ritonavir, commonly referred to as LPV/r, was among the earliest treatments investigated for COVID-19.[35] The rationale behind using this combination was that Ritonavir enhances the bioavailability of Lopinavir by inhibiting cytochrome P450 3A4, an enzyme responsible for metabolizing Lopinavir. This pharmacokinetic boosting effect allows for higher concentrations of Lopinavir in the bloodstream, potentially increasing its antiviral efficacy against SARS-CoV-2.[35]

The effectiveness of Ritonavir, particularly in combination with Lopinavir, has been a subject of extensive clinical research.[41] Early studies on LPV/r in COVID-19 patients yielded mixed results. For instance, a study conducted in Wuhan, China, in early 2020 found no significant difference in the time to clinical improvement between patients treated with LPV/r and those receiving standard care. Similarly, a randomized controlled trial in the United Kingdom, part of the RECOVERY trial, also concluded that LPV/r did not significantly reduce mortality or the duration of hospitalization in COVID-19 patients compared to standard care alone.[42]

However, some studies suggested that LPV/r might offer benefits in certain subsets of patients, particularly when administered early in the course of the disease or in combination with other antiviral agents. A study conducted in Hong Kong found that early triple antiviral therapy, including LPV/r, interferon beta-1b, and ribavirin, was safe and more effective than LPV/r alone in reducing viral load and shortening the duration of symptoms in patients with mild to moderate COVID-19.[34] Despite these promising findings, the overall consensus in the medical community has been cautious, with many experts concluding that Ritonavir, even in combination with Lopinavir,[34] is not a definitive solution for COVID-19 and requires further investigation.

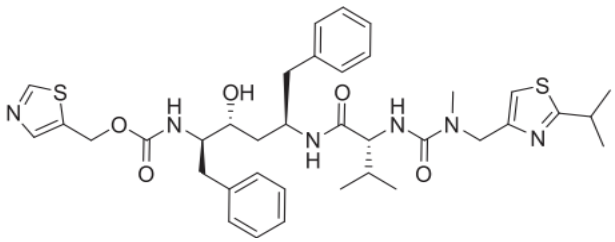

Figure 6. Chemical structure of Ritonavir

CONCLUSION

In conclusion, the Covid-19 spread has created a havoc in all parts of the world and created an emergency for development of suitable cure for this viral infection. The different drugs particularly the anti-viral drugs have shown promise in their application in treatment of Covid-19 to different degree. As most of the studies are hit and trial on predisposition basis, the evaluation reports have different degree of possibility of application of discussed drugs in Covid-19. A thorough and detailed study would provide a better scenario for approved use of specific drug.

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