Newer oral antiviral for the treatment of COVID-19 Infection

1. Abstract

The global Coronavirus disease 2019 (COVID-19) pandemic, caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has indeed seen the emergence of multiple variants. There are several direct-acting antiviral drugs that have been approved or are in process of advancing through clinical development for the treatment of SARS-CoV-2 infection. The oral antiviral medications offer several advantages over intravenous(IV) antivirals, including enhanced safety and the ability to administer during the early stages of the disease to potentially prevent hospitalization. The Food and Drug Administration (FDA) has granted an emergency use authorization (EUA) for an oral antiviral medications Molnupiravir, Nirmatrelvir-Ritonavir and VV116 specially intended for the treatment of mild to moderate COVID-19 in patients at risk of progressing to severe disease. These three mentioned drugs serve different purposes - Molnupiravir is a nucleoside analogue, Nirmatrelvir is a SARS-CoV-2 main protease inhibitor and Ritonavir is used as a protease inhibitor for human immunodeficiency virus type 1. VV116 is a promising oral nucleoside drug candidate with the potential to effectively inhibit SARS-CoV-2 replication, reduce viral RNA levels and limit the presence of infectious virus. The findings are consistent with the observation that the target proteins of the mentioned antiviral drugs, specifically the viral RNA-dependent RNA polymerase and the viral main protease are highly conserved. This suggests that these antivirals may be effective against a broad range of viral strains due to the conservation of their target proteins.

2. Keywords: SARS-CoV-2, Oral antivirals, Molnupiravir, Nirmatrelvir-Ritonavir, VV116

3. Introduction

"Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and illness with the associated coronavirus disease 2019 (Covid-19) continue to threaten global health. Persons with old age, smoking, underlying conditions such as cardiovascular disease, diabetes, obesity and cancer are at high risk for severe Covid-19 and associated adverse outcomes. There is a distinct need of orally effective covid-19 treatments that can prevent the progression of infection, hospitalization and death. Such a measure would help to control the infection very fast and ease the pressure on the health facilities"[1].

"For non-hospitalized patients with mild to moderate covid-19, treatment options include monoclonal antibodies which are effective but require administration and monitoring in a health care setting and there is a possibility of less effectiveness against emerging variants"[1]. "The United State Food and Drug Administration(US-FDA) issued an emergency use authorization(EUA) for the emergency use of the unproven products molnupiravir and nirmatrelvir-ritonavir(paxlovir), both agents are for the treatment of mild to moderate COVID-19 in adults and in pediatric patients and in older who are at risk for progression to severe COVID-19 including hospitalization or death"[2].

In this context, orally effective drugs for covid-19 will be a boon to the clinicians and the patients alike. The current review aims to present the current knowledge about these medicines and predicts the future of these medicine.

3.1 Need for oral agents

"Preventive and curative approaches against Covid-19 will bring significant benefits despite of having some negligible risks. Oral antiviral medications have several advantages over IV antivirals. Safety, treatment in early stages to prevent hospitalization. More importantly, oral medication is the most convenient way for outpatients.

The virus is changing itself and creating new challenges for the efficacy of oral antivirals. Early diagnosis and initiation of treatment are vital success factors for oral antivirals in Covid-19 treatment. Preliminary studies showed that authorized drugs for Covid-19 therapy significantly reduce hospitalization or death among mild to severe patients. We can anticipate that the pandemic phase of Covid-19 might be ended after this massive Omicron waives; however, the Covid-19 will continue"[3].

FDA approved available IV antiviral drugs are Remdesivir and Tocilizumab and FDA approved available Oral antiviral drugs are Molnupiravir, Nirmatrelvir/Ritonavir (Paxlovid) and Baricitinib.

4. Discussion

4.1 Molnupiravir:

"Molnupiravir synthesized at the Emory Institute for Drug Development (EIDD)"[4]. "Molnupiravir is an oral, small-molecule antiviral prodrug that is active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is orally bioavailable prodrug of N4–hydroxycytidine(NHC), which is taken up by cells and phosphorylated to its triphosphate derivative NHC-TP. NHC-TP is incorporated into SARS-CoV-2 RNA by the viral RNA polymerase causing an accumulation of errors in the viral genome and thus inhibits the viral replication"[5]. NHC the analogue of molnupiravir is active in cell culture assays against SARS-CoV2 and has activity against Alpha, Beta, gamma and Delta variants Omicron variant? NHC has been found to be inhibit a range of viruses including chikungunya virus, Venezuelan equine encephalitis virus, respiratory syncytial virus, norovirus influenza A and B viruses, ebola virus and human coronaviruses.

"Molnupiravir is administered orally through 200 mg capsules at a dose of 800 mg every 12 hours, with or without food, for a 5-day period. Repeated or extended courses of therapy are not allowed under the EUA. If a dose is missed, it can be taken within 10 hours of the scheduled time; otherwise, the next dose should be taken as planned without doubling up. No dose adjustments are necessary for geriatric patients based on similar pharmacokinetic data of NHC. The use of molnupiravir hasn't been evaluated in children or adolescents and is not permitted under the EUA. NHC's exposure isn't significantly affected by renal impairment, renal failure, or dialysis, and no adjustments are required. Hepatic elimination isn't a major route for NHC, and no dose adjustments are recommended for liver dysfunction. NHC is metabolized to cytidine and/or uridine through pyrimidine metabolic pathways" [2].

"In phase 2 clinical trials of molnupiravir, no amino acid substitutions related to NHC resistance in SARS-CoV-2 were found. After 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed. NHC displayed effective activity against the virus, even with polymerase substitutions linked to reduced remdesivir sensitivity, suggesting lack of cross-resistance" [2].

"While no clinical drug interaction trials have taken place involving molnupiravir and other medications, existing data indicates that molnupiravir and NHC do not act as substrates, inhibitors, or inducers of several CYP enzymes, human P-glycoprotein (P-gp), or assessed transport proteins. Consequently, there is currently no evidence of drug interactions associated with molnupiravir" [2].

"The safety of molnupiravir was assessed in a phase 3 double-blind trial involving nonhospitalized COVID-19 subjects. The trial included 1411 participants treated with either molnupiravir or placebo for up to 5 days. The most common adverse reactions in the molnupiravir group were diarrhea, nausea, and dizziness, which were similar in both groups. Grade 3 and 4 laboratory abnormalities occurred at a comparable rate in both groups. COVID-19 related serious events were seen in 7% of molnupiravir recipients and 10% of placebo recipients. Death occurred in <1% of molnupiravir subjects and 2% of placebo subjects. Study discontinuation due to adverse events was observed in 1% of those receiving molnupiravir and 3% of those receiving placebo" [2].

4.2 Nirmatrelvir/Ritonavir:

"The US FDA issued and EUA for the emergency use of unproven products Nirmatrelvir Ritonavir, both agents are for the treatment of mild to moderate SARS-Cov-2 in adults and in pediatric patients 12 years of age and older for paxlovid and adults 18 and older who are at risk for progression including hospitalization or death[2]. Nirmatrelvir functions as a SARS-CoV-2 main protease inhibitor (Mpro), which halts the processing of polyprotein precursors and impedes viral replication. Its inhibition of SARS-CoV-2 Mpro is evidenced by a biochemical assay. On the other hand, ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, is used to elevate Nirmatrelvir levels but does not have any effect on SARS-CoV-2 Mpro activity" [1,2].

"Nirmatrelvir displays antiviral efficacy in vitro against SARS-CoV-2, as well as cell culture activity targeting the Alpha, Beta, Gamma, Delta, and Lambda variants[1,6,7]. Its effectiveness against SARS-CoV-2 has been observed in A549-ACE2 cells. While data for its activity against Omicron variants in cell cultures are currently unavailable, Nirmatrelvir has demonstrated activity against Omicron in a biochemical assay" [2].

"The combination of Nirmatrelvir-Ritonavir is available for oral administration as co-packaged 150-mg and 100-mg tablets, respectively. The authorized dosage is 300 mg of Nirmatrelvir and 100 mg of ritonavir every 12 hours for 5 days, with or without food. Repeating or extending treatment courses is not permitted under the EUA. If a dose is missed, it can be taken within 8 hours of the scheduled time; otherwise, the next dose should be taken at the regular time without doubling up. Dose adjustment is not necessary for mild to moderate hepatic impairment (Child-Pugh class A and B). However, the use of Nirmatrelvir-ritonavir is not recommended for individuals with severe hepatic impairment due to limited safety and pharmacokinetic information. Nirmatrelvir is metabolized through the CYP3A4 pathway, but it experiences minimal metabolism and is primarily eliminated through the renal route when co-administered with the CYP3A4 inhibitor ritonavir" [2].

"Nirmatrelvir acts as a substrate and potential inhibitor for P-gp and CYP3A4 enzymes, while Ritonavir functions as a substrate and inhibitor mainly for CYP3A4 and also CYP2D6. Ritonavir induces a range of enzymes, including CYP3A, CYPIA2, CYP2C9, CYP2C19, CYP2B6, and glucuronosyltransferase. The use of Ritonavir is essential to boost Nirmatrelvir levels and is necessary for its effectiveness. Concomitant administration of Nirmatrelvir-Ritonavir with highly dependent substrates mentioned earlier, leading to significant changes in drug concentrations, is contraindicated due to the risk of serious or life-threatening reactions. This also applies to potent CYP inducers, as they might decrease Nirmatrelvir-Ritonavir levels, potentially causing a loss of virologic response and the potential development of resistance" [2].

"The safety profile of Nirmatrelvir-Ritonavir is based on the EPIC-HR trial, a phase 2/3 study involving nonhospitalized high-risk COVID-19 patients. Adverse events were recorded while subjects were on study medication. The Nirmatrelvir-Ritonavir group showed higher adverse event rates with greater frequency (25 subject difference) compared to the placebo group. Common adverse events included dysgeusia, diarrhea, hypertension, and myalgia. The proportions of subjects discontinuing treatment due to adverse events were 2% in the Nirmatrelvir-Ritonavir group and 4% in the placebo group" [1,6,7,8,].

4.3 VV116:

VV116 (JT001) presents itself as a potential COVID-19 treatment, having gained approval for use in Uzbekistan and for clinical trials in China[9,10]. Serving as a deuterated version of remdesivir hydrobromide, VV116 holds promise as a therapeutic option in the ongoing fight against COVID-19[10]. The medicinal chemistry efforts resulted in the discovery of the first deuterated oral RNA-dependent RNA polymerase (RdRp) candidate, VV116. This compound went through significant milestones, evolving from natural nucleosides to the final VV116 form. The proposed mechanism of action of VV116 involves its tri-isobutyrate ester prodrug form, which blocks SARS-CoV-2 RNA replication. The active metabolite VV116-NMP plays a crucial role in inhibiting RNA formation, ultimately preventing the virus's replication process. VV116 shows promising potential as a treatment against SARS-CoV-2 due to its unique mechanism of action and its ability to hinder viral RNA replication[9,11].

VV116 stands out as an oral antiviral agent with high potency against SARS-CoV-2 variants (alpha, beta, delta and omicron). It's hydrobromide form offers good oral bioavailability and strong effectiveness against the virus, making it a promising candidate for combatting SARS-CoV-2[9,12,13,14].

Research has confirmed the high bioavailability and wide distribution of VV116 across various tissues. Studies by Qian et al showed that VV116's primary metabolite 116-N1 rapidly reached peak plasma concentration after oral administration, indicating swift hydrolysis to 116-N1. Additionally, Zhou findings suggested dose-dependent relationships between parameters like AUC and C_{max} within the 25 to 800 mg dose range, with potential saturation in drug absorption at 800 mg. The mean $T_{1/2}$ of VV116 varied based on doses, hinting at the possibility of exploring 2 to 3 daily doses in clinical trials. Repeated doses in the MAD study demonstrated cumulative AUC and Cmax values, maintaining effective antiviral levels across different dosage groups. The effect of diet was studied, revealing that VV116's administration under fasting or normal diet conditions was preferable due to its potential interaction with high-fat diets. In conclusion, these findings highlight VV116's promising pharmacokinetic profile and its potential for effective use against SARS-CoV-2[9,10].

Pharmacokinetic profile, interaction and its potential for effective use against SARS-CoV-2. against SARS-CoV-2. This drug is in under clinical trial. Among those in the VV116 group, there were 9 reported adverse events, none of which were serious. Most of these events involved mild liver function issues, and they were all resolved without further treatment. Additionally, there were less frequent adverse events related to elevated blood urea and white blood cell count. Overall, the study indicates that the VV116 group experienced relatively mild and manageable adverse events. During the analysis, it was observed that participants in the food-effect subgroup experienced a higher occurrence of adverse events (AEs) when they were under the high-fat meal condition. This indicates that the type of meal consumed could have an impact on the incidence of adverse events[9,10,13].

4.4 Comparison of VV116 and Nirmatrelvir–Ritonavir:

"Nirmatrelvir–Ritonavir has been authorized for emergency use by many countries for the treatment of coronavirus disease 2019 (Covid-19). However, the supply falls short of the global demand, which creates a need for more options. VV116 is an oral antiviral agent with potent activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).Early administration of oral VV116 was noninferior to Nirmatrelvir–Ritonavir in shortening the time to sustained clinical recovery in participants (among the adults) with mild-to-moderate Covid-19 who were at high risk for progression to severe disease. VV116 also had fewer safety concerns than Nirmatrelvir–Ritonavir" [8].

4.5 Other antiviral drugs:

Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2:

"Here, screened approximately 18,000 drugs for antiviral activity using live virus infection in human respiratory cells and validated 122 drugs with antiviral activity and selectivity against SARS-CoV-2. Among these candidates are 16 nucleoside analogues, the largest category of clinically used antivirals. This included the antivirals Remdesivir and Molnupiravir, which have been approved for use in COVID-19. RNA viruses rely on a high supply of nucleoside triphosphates from the host to efficiently replicate, and we identified a panel of host nucleoside biosynthesis inhibitors as antiviral. Moreover, we found that combining pyrimidine biosynthesis inhibitors with antiviral nucleoside analogues synergistically inhibits SARS-CoV-2 infection in vitro and in vivo against emerging strains of SARS-CoV-2"[15].

Other Investigational Antivirals are:

Obeldesivir(GS-5245):

GS-5245 or Obeldesivir (ODV), demonstrates broad-spectrum antiviral activity against various coronaviruses, including SARS-CoV, MERS-CoV, SARS-CoV-2, and related strains, both in vitro and in mouse

models. This efficacy is attributed to its targeting of the highly conserved RNA-dependent viral RNA polymerase (RdRp)[16].

Ensitrelvir:

Ensitrelvir, developed by Shionogi, represents a significant advancement as the first oral noncovalent, nonpeptide inhibitor. Its rapid clearance of SARS-CoV-2 in a phase 2/3 clinical trial, coupled with its favorable tolerability profile, led to emergency authorization in Japan. This underscores its potential as a promising treatment option for combating COVID-19[17]. The antiviral efficacy and safety of ensitrelvir, a novel oral SARS-CoV-2 3CL protease inhibitor, in patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection, showed promising results. Despite the majority of enrolled patients being vaccinated, ensitrelvir demonstrated significant antiviral efficacy with a 5-day oral administration regimen, leading to rapid reduction in viral titer and viral RNA levels. These findings suggest ensitrelvir holds potential as an effective treatment option for COVID-19 patients in real-world scenarios[18].

Bucillamine:

Research conducted at the University of California, San Francisco suggests that thiol drugs like bucillamine may have potential antiviral and prophylactic effects by preventing the binding of the virus to ACE2 receptors. While the drug's primary focus has been on its antioxidant and anti-inflammatory properties, its past role as a potent anti-inflammatory agent could benefit COVID-19 patients, particularly those experiencing inflammation. This underscores the multifaceted potential of bucillamine in combating COVID-19[19].

Opaganib:

Opaganib is an oral treatment under investigation[20]. opaganib exhibits antiviral activity against various viruses, including SARS-CoV-2. The completion of a multinational Phase 2/3 clinical trial showed that opaganib can be safely administered to hospitalized COVID-19 patients. Importantly, the trial revealed a significant 62% decrease in mortality among a large subgroup of patients with moderately severe COVID-19, indicating the potential of opaganib as a promising therapeutic option for managing severe cases of the disease[21]. Opaganib represents a significant advancement as an oral, first-in-class selective inhibitor of sphingosine kinase 2 (SK2)[20]. Opaganib exerts its effects by inhibiting three key enzymes involved in sphingolipid metabolism: sphingosine kinase-2 (SK2), dihydroceramide desaturase (DES1), and glucosylceramide synthase (GCS). This multifaceted inhibition demonstrates its potential as a versatile therapeutic agent for targeting various diseases and underscores its broad applicability in treating conditions beyond COVID-19[21].

Sabizabulin(VERU-111):

Sabizabulin (VERU-111) is an oral small molecule tubulin inhibitor developed by Veru, exhibiting potential anti-tumor, antiviral, and anti-inflammatory activities. As a new candidate drug for COVID-19, its multifaceted properties make it a promising option for addressing various aspects of the disease, ranging from viral replication inhibition to immune modulation[22].

Bemnifosbuvir(BEM, AT-527):

Bemnifosbuvir (BEM, AT-527) represents a novel oral guanosine nucleotide antiviral drug for treating COVID-19 patients. To ensure effective treatment, it's essential to directly assess drug disposition in the lungs through bronchoalveolar lavage, thereby ensuring adequate antiviral drug levels at the primary site of SARS-CoV-2 infection. This approach is crucial for optimizing therapeutic outcomes and combating the virus effectively[23]. Bemnifosbuvir, an oral antiviral drug with a dual mechanism of action targeting viral RNA polymerase, has shown promising in vitro activity against SARS-CoV-2. Our phase 2 double-blind study aimed to assess its antiviral activity, safety, efficacy, and pharmacokinetics in ambulatory patients with mild to moderate COVID-19[24].

Clinical trials of existing drugs with antiviral properties are:

Nitazoxanide:

Nitazoxanide (NTZ) possesses significant anti-inflammatory and immunological properties that may help alleviate complications caused by SARS-CoV-2 infection, recent studies have not definitively demonstrated its direct anti-SARS-CoV-2 effect. Therefore, further research is warranted to fully evaluate the potential beneficial outcomes of NTZ in the treatment of COVID-19[25].

Niclosamide:

Niclosamide has demonstrated multiple mechanisms of action against SARS-CoV-2, including neutralizing endolysosomal pH to prevent cell entry, inhibiting RNA viruses during replication, and preventing viral replication through the inhibition of SARS-CoV-2 spike protein-mediated cell fusion. These findings highlight the potential of Niclosamide as a promising therapeutic agent for combating COVID-19[26].

ATV006:

"Report saws that esterification of the 5′-hydroxyl moieties of GS-441524 markedly improved antiviral potency. This 5′-hydroxyl-isobutyryl prodrug, ATV006, demonstrated excellent oral bioavailability in rats and cynomolgus monkeys and exhibited potent antiviral efficacy against different SARS-CoV-2 VOCs in vitro and in three mouse models. Oral administration of ATV006 reduced viral loads and alleviated lung damage when administered prophylactically and therapeutically to K18-hACE2 mice challenged with the Delta variant of SARS-CoV-2. These data indicate that ATV006 represents a promising oral antiviral drug candidate for SARS-CoV-2"[27].

5. Conclusion

This study showed that the oral antivirals are reduced the risk of hospitalization or death in at-risk, infection with SARS-CoV-2 and illness with the associated Covid-19. This oral antiviral drugs Molnupiravir and Nirmatrelvir-Ritonavir(paxlovid) are FDA approved drugs. It has several advantages over IV antiviral drugs. Initial trials suggested greater efficacy of paxlovid, but recent studies indicated comparable potency in older adults. These all above data shows that, both drugs have similar efficacy in older adults and inform on possible epidemiologic benefit of antiviral treatment. Other than these drugs Remdesivir IV antiviral drug is also effective in the treatment of SARS-CoV-2 and Covid-19. Oral Remdesivir derivative VV116 (serving as a deuterated Version) holds promise as a therapeutic option in the ongoing fight against Covid-19.

Other antiviral drugs are also available, in these investigational antivirals are Obeldesivir, Ensitrelvir, Bucillamine, JT001(formerly VV116), Opaganib, Sabizabulin, Bemnifosbuvir. The clinical trials of existing drugs with antiviral properties include Nitazoxanide and Niclosamide. ATV006 also an antiviral drug and it represents a promising oral antiviral drug candidate for SARS-CoV-2.

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References

1. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, Pypstra R. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. New England Journal of Medicine. 2022 Apr 14;386(15):1397-408.
2. Saravolatz LD, Depcinski S, Sharma M. Molnupiravir and nirmatrelvir-ritonavir: oral coronavirus disease 2019 antiviral drugs. Clinical Infectious Diseases. 2023 Jan 1;76(1):165-71.
3. Islam T, Hasan M, Rahman MS, Islam MR. Comparative evaluation of authorized drugs for treating Covid-19 patients. Health Science Reports. 2022 Jul;5(4):e671.
4. Whitley R. Molnupiravir—a step toward orally bioavailable therapies for Covid-19. New England Journal of Medicine. 2022 Feb 10;386(6):592-3.
5. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. New England Journal of Medicine. 2022 Feb 10;386(6):509-20.
6. Arbel R, Wolff Sagy Y, Hoshen M, Battat E, Lavie G, Sergienko R, Friger M, Waxman JG, Dagan N, Balicer R, Ben-Shlomo Y. Nirmatrelvir use and severe Covid-19 outcomes during the Omicron surge. New England Journal of Medicine. 2022 Sep 1;387(9):790-8.
7. Chen BS, Hung CH, Wei JC. Nirmatrelvir for nonhospitalized adults with Covid-19. NEW ENGLAND JOURNAL OF MEDICINE. 2022 Aug 4;387(5):474-.
8. Cao Z, Gao W, Bao H, Feng H, Mei S, Chen P, Gao Y, Cui Z, Zhang Q, Meng X, Gui H. VV116 versus nirmatrelvir–ritonavir for oral treatment of Covid-19. New England Journal of Medicine. 2023 Feb 2;388(5):406-17.
9. Qian HJ, Wang Y, Zhang MQ, Xie YC, Wu QQ, Liang LY, Cao Y, Duan HQ, Tian GH, Ma J, Zhang ZB. Safety, tolerability, and pharmacokinetics of VV116, an oral nucleoside analog against SARS-CoV-2, in Chinese healthy subjects. Acta Pharmacologica Sinica. 2022 Dec;43(12):3130-8.
10. Xiao N, Huang X, Kang X, Zang W, Li B, Kiselev S. The safety and efficacy of oral antiviral drug VV116 for treatment of COVID-19: a systematic review. Medicine. 2023 Jul 7;102(27):e34105.
11. Xie Y, Yin W, Zhang Y, Shang W, Wang Z, Luan X, Tian G, Aisa HA, Xu Y, Xiao G, Li J. Design and development of an oral remdesivir derivative VV116 against SARS-CoV-2. Cell research. 2021 Nov;31(11):1212-4.
12. Yang L, Wang Z. Bench-to-bedside: Innovation of small molecule anti-SARS-CoV-2 drugs in China. European Journal of Medicinal Chemistry. 2023 May 18:115503.
13. Shen Y, Ai J, Lin N, Zhang H, Li Y, Wang H, Wang S, Wang Z, Li T, Sun F, Fan Z. An open, prospective cohort study of VV116 in Chinese participants infected with SARS-CoV-2 omicron variants. Emerging microbes & infections. 2022 Dec 31;11(1):1518-23.
14. Schäfer A, Martinez DR, Won JJ, Meganck RM, Moreira FR, Brown AJ, Gully KL, Zweigart MR, Conrad WS, May SR, Dong S. Therapeutic treatment with an oral prodrug of the remdesivir parental nucleoside is protective against SARS-CoV-2 pathogenesis in mice. Science Translational Medicine. 2022 Mar 22;14(643):eabm3410.

15. Schultz DC, Johnson RM, Ayyanathan K, Miller J, Whig K, Kamalia B, Dittmar M, Weston S, Hammond HL, Dillen C, Ardanuy J. Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2. Nature. 2022 Apr 7;604(7904):134-40.
16. Martinez DR, Moreira FR, Zweigart MR, Gully KL, De la Cruz G, Brown AJ, Adams LE, Catanzaro N, Yount B, Baric TJ, Mallory ML. Efficacy of the oral nucleoside prodrug GS-5245 (Obeldesivir) against SARS-CoV-2 and coronaviruses with pandemic potential. bioRxiv. 2023 Jun 28.
17. Lin M, Zeng X, Duan Y, Yang Z, Ma Y, Yang H, Yang X, Liu X. Molecular mechanism of ensitrelvir inhibiting SARS-CoV-2 main protease and its variants. Communications Biology. 2023 Jul 5;6(1):694.
18. Mukae H, Yotsuyanagi H, Ohmagari N, Doi Y, Imamura T, Sonoyama T, Fukuhara T, Ichihashi G, Sanaki T, Baba K, Takeda Y. A randomized phase 2/3 study of ensitrelvir, a novel oral SARS-CoV-2 3C-like protease inhibitor, in Japanese patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection: results of the phase 2a part. Antimicrobial agents and chemotherapy. 2022 Oct 18;66(10):e00697-22.
19. Frank M. Bucillamine in the treatment of patients with mild to moderate COVID-19: an interview with Michael Frank. Future Microbiology. 2022 Jan;17(3):157-9.
20. Carvalho Neuenschwander F, Barnett-Griness O, Piconi S, Maor Y, Sprinz E, Assy N, Khmelnitskiy O, Lomakin N, Goloshchekin BM, Nahorecka E, Calvacante AJ. Effect of Opaganib on Supplemental Oxygen and Mortality in Patients with Severe SARS-CoV-2 Pneumonia. medRxiv. 2022:2022-06.
21. Smith CD, Maines LW, Keller SN, Katz Ben-Yair V, Fathi R, Plasse TF, Levitt ML. Recent Progress in the Development of Opaganib for the Treatment of Covid-19. Drug Design, Development and Therapy. 2023 Dec 31:2199-211.
22. Zeng Z, Liao C, Yu L. Molecules for COVID-19 treatment. Chinese Chemical Letters. 2023 Dec 2:109349.
23. Title: Human bronchopulmonary disposition and plasma pharmacokinetics of oral 2 bemnifosbuvir (AT-527), an experimental guanosine nucleotide prodrug for COVID-1.
24. Boffito M, Dolan E, Singh K, Holmes W, Wildum S, Horga A, Pietropaolo K, Zhou XJ, Clinch B, Collinson N, Ukachukwu V. A Phase 2 Randomized Trial Evaluating the Antiviral Activity and Safety of the Direct-Acting Antiviral Bemnifosbuvir in Ambulatory Patients with Mild or Moderate COVID-19 (MOONSONG Study). Microbiology Spectrum. 2023 Jun 20:e00077-23.
25. Al-Kuraishy HM, Al-Gareeb AI, Elekhnawy E, Batiha GE. Nitazoxanide and COVID-19: a review. Molecular biology reports. 2022 Nov;49(11):11169-76.
26. Kouira O, Bayoudh S, Smati H, Bouzid M, Aouaini F, Lamine AB. Physicochemical modeling and characterization of the adsorption mechanism of seven pharmaceutical molecules onto SARS-CoV-2 virus. Materials Chemistry and Physics. 2023 Oct 1;307:128219.
27. Cao L, Li Y, Yang S, Li G, Zhou Q, Sun J, Xu T, Yang Y, Liao R, Shi Y, Yang Y. The adenosine analog prodrug ATV006 is orally bioavailable and has preclinical efficacy against parental SARS-CoV-2 and variants. Science Translational Medicine. 2022 May 17;14(661):eabm7621.