Review Article

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.Several direct-acting antiviral drugs have been approved or are in the process of being developed for the treatment of SARS-CoV-2 infection.Oral antiviral medications offer several advantages over intravenous (IV) antivirals, including enhanced safety and the ability to be administered during the early stages of the disease to potentially prevent hospitalization.The Food and Drug Administration (FDA) has granted emergency use authorization (EUA) for the oral antiviral medications Molnupiravir, Nirmatrelvir-Ritonavir, and VV116, specifically intended for the treatment of mild to moderate COVID-19 in patients at risk of progressing to severe disease.These three 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. It has been observed that the target proteins of these 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 the associated coronavirus disease 2019 (COVID-19) continue to threaten global health.
People with old age, smoking history, 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 for orally effective COVID-19 treatments that can prevent disease progression, hospitalization, and death. Such a measure would help to control the infection very quickly and ease the pressure on healthcare 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 healthcare setting. Additionally, there is a possibility of reduced effectiveness against emerging variants. [1]

The United States Food and Drug Administration (FDA) initially issued an emergency use authorization (EUA) for molnupiravir and nirmatrelvir-ritonavir (Paxlovid). Both agents are for the treatment of mild to moderate COVID-19 in adults and pediatric patients 12 years and older who are at risk for progression to severe COVID-19, including hospitalization or death. [2] Laterin May 2023, nirmatrelvir-ritonavir (Paxlovid) received full FDA approval.
In this context, orally effective drugs for COVID-19 would be a boon to both clinicians and patients.The current review aims to present the current knowledge about these medicines and predict their future.

3.1 Need for oral agents

Preventive and curative approaches against COVID-19 will bring significant benefits despite some negligible risks. Oral antiviral medications have several advantages over intravenous (IV) antivirals, such as safety and the ability to be administered in the early stages to prevent hospitalization. More importantly, oral medication is the most convenient option for outpatients.The virus is rapidly changing and creating new challenges for the efficacy of oral antivirals. Early diagnosis and early initiation of treatment are vital factors for the success of oral antivirals in COVID-19 treatment.Preliminary studies have shown that authorized drugs for COVID-19 therapy significantly reduce hospitalization or death among patients with mild to severe illness.We can anticipate that the pandemic phase of COVID-19 may have ended after these massive Omicron waves; however, COVID-19 infections will likely continue.

4. Discussion

4.1 Molnupiravir

Molnupiravir, synthesized at the Emory Institute for Drug Development (EIDD) [4], is an orally bioavailable prodrug of N4-hydroxycytidine (NHC). This small-molecule antiviral medication is active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Cells take up NHC, a phosphorylated form of molnupiravir, which is then incorporated into viral RNA by the SARS-CoV-2 RNA polymerase. This incorporation leads to errors in the viral genome, inhibiting viral replication [5].

In cell culture assays, NHC, the active analog of molnupiravir, demonstrates activity against SARS-CoV-2 and other viruses, including Alpha, Beta, Gamma, and Delta variants. Data on the Omicron variant's susceptibility is currently unavailable. Additionally, NHC has shown effectiveness against a wider 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 as 200 mg capsules at a dose of 800 mg every 12 hours, with or without food, for a 5-day period. The Emergency Use Authorization (EUA) does not allow for repeated or extended courses of therapy. If a dose is missed within 10 hours of the scheduled time, it can be taken. 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 has not been evaluated in children or adolescents and is not permitted under the EUA. NHC exposure is not significantly affected by renal impairment, renal failure, or dialysis, and no adjustments are required. Hepatic elimination is not 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].

Phase 2 clinical trials of molnupiravir did not find any amino acid substitutions related to NHC resistance in SARS-CoV-2. 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 a lack of cross-resistance [2].

While no clinical drug interaction trials have been conducted involving molnupiravir and other medications, existing data suggests 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].

A phase 3 double-blind trial involving nonhospitalized COVID-19 subjects assessed the safety of molnupiravir. 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 less than 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 initially issued EUA for the emergency use of the Nirmatrelvir and Ritonavir combination in December 2021. Later in May 2023, the US FDA approved this combination for the treatment of mild-to-moderate SARS-CoV-2 infection in adults and pediatric patients 12 years of age and older who are at risk for progression to severe disease, including hospitalization or death [2].

Nirmatrelvir functions as a SARS-CoV-2 main protease inhibitor (Mpro), halting the processing of polyprotein precursors and impeding viral replication. A biochemical assay demonstrates its inhibition of SARS-CoV-2 Mpro. Ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, is used to boost Nirmatrelvir levels but has no effect on SARS-CoV-2 Mpro activity [1,2].

Nirmatrelvir displays antiviral efficacy in vitro against SARS-CoV-2, with 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 Nirmatrelvirand 100 mg of ritonavir every 12 hours for 5 days, with or without food. Repeating or extending treatment courses is not permitted. 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 undergoes 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. Ritonavir functions as a substrate and inhibitor mainly for CYP3A4 and also CYP2D6. Ritonavir induces a range of enzymes, including CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2B6, and glucuronosyltransferase. Because ritonavir is essential to boost Nirmatrelvir levels, it is necessary for the drug's effectiveness. Concomitant administration of Nirmatrelvir-Ritonavir with highly dependent substrates or potent CYP inducers is contraindicated due to the risk of serious or life-threatening reactions or a loss of virologic response and potential development of resistance [2].

4.3 VV116

VV116 (JT001) is a potential treatment for COVID-19, approved for use in Uzbekistan and clinical trials in China [9,10]. As a deuterated version of remdesivir hydrobromide, VV116 holds promise as a therapeutic option in the fight against COVID-19 [10]. Medicinal chemistry efforts led to the discovery of VV116, the first deuterated oral RNA-dependent RNA polymerase (RdRp) inhibitor. This compound underwent significant development, evolving from natural nucleosides to its final form. VV116's proposed mechanism of action involves its tri-isobutyrate ester prodrug form, which blocks SARS-CoV-2 RNA replication. The active metabolite, VV116-NMP, plays a crucial role by inhibiting RNA formation, ultimately preventing viral replication [9,11]. VV116 shows promising potential due to its unique mechanism of action and ability to hinder viral RNA replication [9,11].

Key points:

- VV116 is an orally available antiviral agent with high potency against various SARS-CoV-2 variants (alpha, beta, delta, and omicron) [9, 12, 13, 14].
- Its hydrobromide form offers good oral bioavailability and strong effectiveness against the virus [9, 12, 13, 14].
- Research confirms high bioavailability and wide distribution of VV116 across various tissues [9, 10].
- Studies suggest a favorable pharmacokinetic profile, with potential for effective use against SARS-CoV-2 [9, 10].
- Clinical trials show VV116 to be well-tolerated, with mostly mild and manageable side effects [9, 10, 13].
- High-fat meals may increase the incidence of adverse events [9, 10, 13].

Note:

- Removed unnecessary repetition.
- Combined similar sentences for better flow.
- Bolded key points for easier reference.

4.4 Comparison of VV116 and Nirmatrelvir–Ritonavir:

Nirmatrelvir-Ritonavir, though authorized for emergency use in many countries for COVID-19 treatment, faces supply limitations. VV116, a potent oral antiviral against SARS-CoV-2, offers promise. Early use of VV116 was found to be noninferior to Nirmatrelvir-Ritonavir in shortening recovery time for high-risk adults with mild-to-moderate COVID-19, with fewer safety concerns [8].

4.5 Other investigational antiviral drugs:
Following are the candidate drugs in this group:

Obeldesivir (GS-5245): Obeldesivir (ODV), also known as GS-5245, 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 Pharmaceuticals, 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 use 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 titre 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 in a 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].

Nitazoxanide: Nitazoxanide (NTZ), an existing antiprotozoal drug, 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, an existing antihelminthic drug, 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: Research indicates 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

In conclusion, the development and approval of orally effective antiviral drugs like Molnupiravir and Nirmatrelvir-Ritonavir represent significant milestones in the ongoing battle against COVID-19. These medications offer promising options for both preventive and curative approaches, particularly for non-hospitalized patients with mild to moderate symptoms. Their oral administration, coupled with favorable safety profiles and demonstrated efficacy against various SARS-CoV-2 variants, underscores their potential to alleviate the

burden on healthcare systems and improve outcomes for individuals at risk of severe disease. Additionally, ongoing research into investigational antiviral drugs such as VV116, Obeldesivir, Ensitrelvir, and others highlights the continuous efforts to expand treatment options and combat emerging challenges posed by the virus. As the pandemic evolves, these developments offer hope for more effective management strategies against COVID-19 and its potential future interactions.

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 PharmacologicaSinica. 2022 Dec;43(12):3130-8.
10. Xiao N, Zang W, Sergey K. The Safety and Efficacy of Oral Antiviral Drug VV116 for Treatment of COVID-19: A Systematic Review.
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. Zhou XJ, Horga A, Puri A, Winchester L, Montrond M, Pietropaolo K, Belanger B, Fletcher CV, Hammond J. Human bronchopulmonary disposition and plasma pharmacokinetics of oral bemnifosbuvir (AT-527), an experimental guanosine nucleotide prodrug forCOVID-19. MedRxiv.2024:2024-01.
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.