Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU30258

# *Review of COVID-19 Therapeutic Drugs and Their Mechanisms: Taking Molnupiravir and Paxlovid as Examples*

**Weite Wang**

*Department of Chemical and Environmental Engineering, University of Nottingham Ningbo, Ningbo, China*
*ssyww3@nottingham.ac.uk*

***Abstract.*** The worldwide dissemination of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the COVID-19 pandemic, which continues to present a global threat to both healthcare workers and the wider public. Beyond the acute disease phase, many patients suffer residual symptoms ("long COVID") compromising their quality of life and functional capacity. Therefore, efficacious oral antivirals that can be given early in the course have emerged as must-have tools to avert progression of severe disease, prevent hospitalizations, and perhaps avoid long-term sequela. In this review, we have collated mechanistic and clinical data for two of the oral antivirals that are widely used currently – Molnupiravir and Paxlovid (Nirmatrelvir/Ritonavir) – using only sources and citations that appear in the project materials. The article summarizes for each agent, chemical identity, pharmacological mechanism, pharmacokinetic considerations, clinical performance, and safety concerns. Comparisons of strengths and limitations are discussed about mechanism-based clinical decision making. Inline figures from original project files (chemical structures and mechanistic diagrams) have been included and should be included at the placeholders when preparing the final Word document. We finish the discussion with implications for therapeutic choice and outline topics for future work.

***Keywords:*** COVID-19, SARS-CoV-2, Molnupiravir, Paxlovid, Nirmatrelvir, Ritonavir, antiviral mechanism, drug–drug interactions

## 1. Introduction

The clinical spectrum of COVID-19 ranges from asymptomatic infection to severe disease, potentially leading to respiratory failure and multiorgan dysfunction. Outside of the acute phase, some patients have persistent symptoms that last a minimum of 12 weeks, i.e., long COVID, including fatigue, dyspnea, persistent cough, chest pain, cognitive impairment, sensory alterations (e.g., anosmia), memory issues, headaches, myalgia, etc. Several comorbidities, such as asthma, type 1 and type 2 diabetes mellitus, and peripheral and coronary heart disease, were identified in patients who developed serious disease. Cytokine-induced cytotoxicity or immune-mediated can also present with asthenia, fatigue, dyspnea, weight loss, abnormalities in hemostasis, coagulation, liver injury, neuropsychiatric symptoms including anosmia, headache, musculoskeletal complaints, gastrointestinal symptoms, rash, dermatologic phenomena, hair loss, and thromboembolism. Organ

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DOI: 10.54254/2753-8818/2025.AU30258

involvement has been reported involving cardiac failure, arrhythmias, and thromboembolic events, along with severe ongoing respiratory disease (aggravated asthma and chronic obstructive pulmonary disease, COPD [1]. The heterogeneity of these sequelae points to a multifactorial pathophysiology, which likely includes residual viral antigen, immune dysregulation, organ damage from the acute disease, and other host factors.

Because persistent viral replication in the nasopharynx or reservoirs has been proposed as a potential contributor to prolonged symptoms, early antiviral therapy that reduces viral load and shortens the duration of viral replication may not only prevent severe acute outcomes but also decrease the risk or severity of long COVID [2]. As such, oral antivirals that can be readily administered in outpatient settings—most notably Molnupiravir and Paxlovid—have become central to clinical management algorithms for at-risk patients. This review focuses on these two agents, integrating mechanistic details and available clinical evidence to inform rational use.

## 2. Global impact of COVID-19: morbidity, mortality and socioeconomics

The disease's toll is not just to clinical mortality, but to long-lasting damage to health systems and economies. Population-level evaluations suggest higher 1-year mortality among age- and comorbidity-burdened populations [3]. Economically, disruption of supply chains, widespread tourism and trade decline, and service-sector losses took hold; the multi-billion-dollar loss in tourism was estimated by the World Tourism Organization as early as 2020. The concomitant health and economic burden highlights the importance of timely, efficacious, and available therapeutics that limit hospitalization and save health care capacity [4]. Available on-patient antivirals, help both the patient and public-health goals of curbing severe disease and alleviating the hospital burden [2].

## 3. Viral pathogenesis and host immune response (mechanistic background)

SARS-CoV-2 is a positive-sense RNA virus with an envelope, and its cellular entry occurs when the spike (S) glycoprotein binds to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells [5]. Organs and tissues that express ACE2 abundantly—such as the respiratory epithelium, vascular endothelium, and segments of the gastrointestinal tract—are particularly vulnerable, accounting for the broad systemic manifestations of the infection [5]. After receptor attachment and internalization, the viral RNA undergoes translation and replication through the RNA-dependent RNA polymerase (RdRp) encoded by the virus, while cleavage of viral polyproteins by proteases, most notably the 3C-like protease (3CL^pro), is crucial for the production of non-structural proteins required to assemble the replication complex [6,7]. Innate immunity recognizes viral components via pattern recognition receptors (PRRs), initiating interferon and inflammatory responses; however, SARS-CoV-2 has evolved mechanisms to blunt early interferon signaling and to evade antigen presentation, facilitating unchecked replication in some hosts and contributing to severe disease phenotypes [5,7]. These mechanistic insights directly inform antiviral strategies: blockade of protease activity (to prevent polyprotein processing) and interference with RdRp-mediated replication (to induce lethal mutagenesis) target essential and mechanistically distinct steps in the viral life cycle, providing complementary therapeutic approaches.

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## 4. Molnupiravir — chemistry, mechanism and safety considerations

### 4.1. Chemical identity and physical-chemical properties

As seen in the Figure, Molnupiravir is an orally bioavailable prodrug of the ribonucleoside analog N-hydroxycytidine (NHC). The compound's IUPAC name is (2R,3S,4R,5R)-3,4-dihydroxy-5-[(4-hydroxyamino)-2-oxopyrimidin-1(2H)-yl]oxolan-2-yl)methyl isobutyrate, with a molecular weight ~329.31 $g \cdot mol^{-1}$ and multiple hydrogen-bond donors and acceptors appropriate for nucleoside analogs [8].

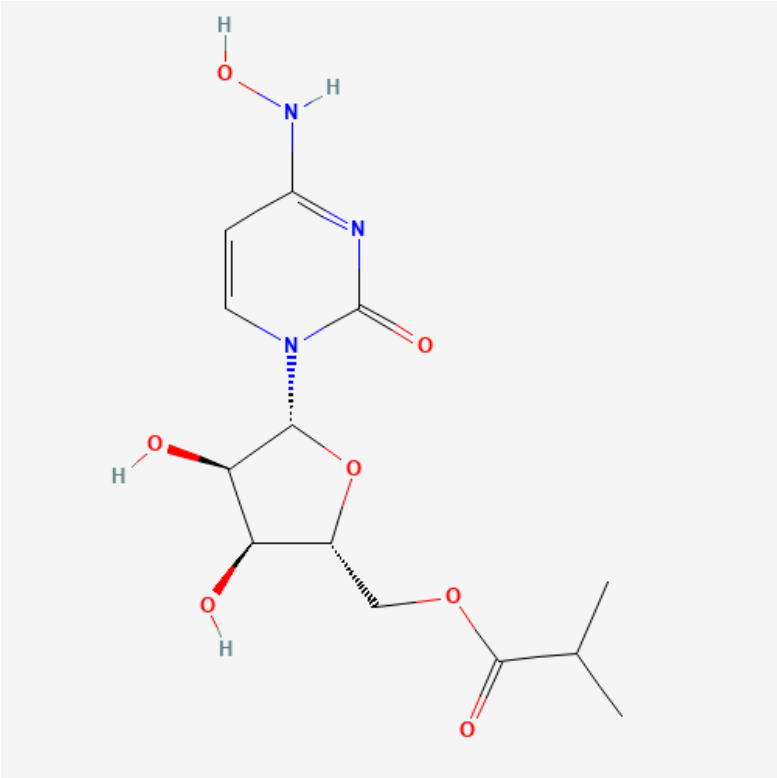



Figure 1. The structure of Molnupiravir (PubChem, 2025)

### 4.2. Mechanism of antiviral action

Molnupiravir is metabolized in vivo to NHC and further phosphorylated to NHC-triphosphate (NHC-TP), the active species recognized by SARS-CoV-2 RdRp [7; Maas et al.,2022). When incorporated into nascent viral RNA, NHC causes base-pairing ambiguity—i.e., it can pair with either guanosine or adenosine—thereby introducing mutations during replication. Accumulation of these mutations leads to "error catastrophe," a state in which the viral population accrues lethal mutational burden and replication collapses [7]. Because this mechanism acts on the replication machinery's fidelity rather than a discrete viral protein binding pocket, it confers broad-spectrum potential against diverse RNA viruses while relying on sustained incorporation into replicating viral genomes.

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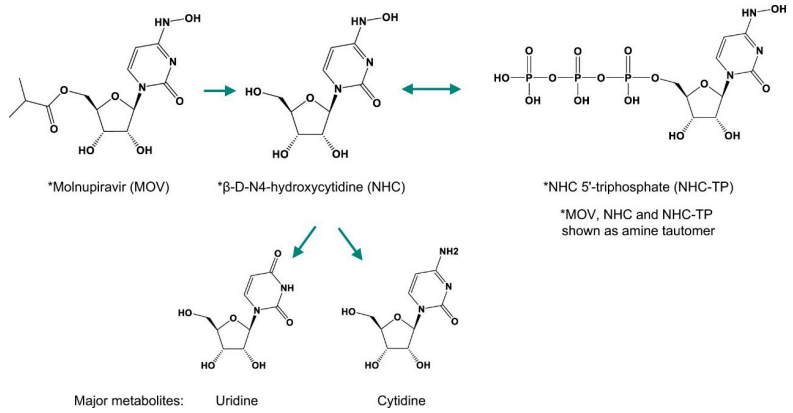



Figure 2. Molnupiravir changes within the human body [7]

### 4.3. Pharmacology and clinical evidence

Molnupiravir is administered orally, and the systemic exposure supports its antiviral effects in preclinical and clinical studies [7]. Clinical trials have shown reductions in viral RNA and –in certain trials – reductions in hospitalizations for some cohorts of patients, although pooled head to head meta-analyses indicate that Molnupiravir's efficacy impact on hospitalization and death is overall less than that achieved with nirmatrelvir/ritonavir (Paxlovid) when both drugs are administered to similar high-risk outpatient cohorts [2,9].

### 4.4. Safety and toxicology considerations

Since Molnupiravir causes mutagenesis to the viral RNA, there has been preclinical interest in the genotoxicity to hosts. An extensive molnupiravir genotoxicity and carcinogenicity evaluation it has shown that host DNA is exposed to NHC in different modelled conditions; however, the dosing regimens in clinical practice for COVID-19 are chosen so that a meaningful risk of genotoxicity to hosts is minimized. The question of risk to host genotoxicity is still under study and investigation by regulatory authorities [10]. Thus, physicians need to consider the advantages of Molnupiravir versus potential long-term adverse effects, particularly in populations for which other, mutagenic, mechanism-less agents might be available.

## 5. Paxlovid (Nirmatrelvir + Ritonavir): protease inhibition with pharmacokinetic boosting

### 5.1. Composition and chemical identity

Paxlovid contains nirmatrelvir (potent inhibitor of SARS-CoV-2 3CL protease) in co-formulation with ritonavir, a pharmacokinetic enhancer, an inhibitor of cytochrome P450 3A4 (CYP3A4), hence prolonging nirmatrelvir systemic exposure [11,12]. The main properties and chemical structure are available as shown in the Figure 2.

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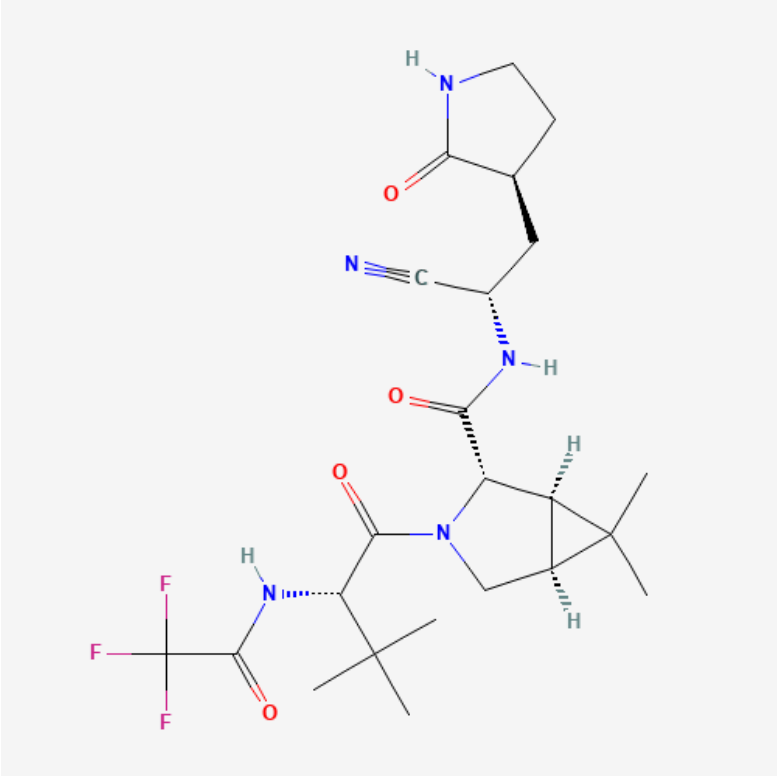



Figure 3. Structure of Nirmatrelvir [11]

## 5.2. Mechanism of antiviral activity

Nirmatrelvir targets the viral 3C-like protease (3C $L^{pro}$ , also called $M^{pro}$ ), an essential cysteine protease that catalyzes the proteolytic cleavage of viral polyproteins (pp1a and pp1ab) into the functional non-structural proteins (nsps) necessary for replication complex assembly [6]. The catalytic machinery of 3C $L^{pro}$ is composed of a catalytic dyad—cysteine (Cys145) and histidine (His41)—which cooperate to hydrolyze peptide bonds at specific sites in the viral polyprotein.

As illustrated in Figure 4, the proteolytic reaction proceeds through several coordinated steps:

1. Step I – Activation of the nucleophile: The imidazole side chain of His41 abstracts a proton from the thiol group of Cys145, generating a highly nucleophilic thiolate anion.

2. Step II – Nucleophilic attack: This thiolate attacks the carbonyl carbon of the scissile peptide bond (R–CO–NH–R'), forming a tetrahedral thiohemiketal intermediate stabilized by the enzyme's oxyanion hole.

3. Step III – Peptide bond cleavage: Collapse of the tetrahedral intermediate releases the amine leaving group (R'-$NH_2$) and forms an acyl–enzyme thioester intermediate between Cys145 and the substrate carbonyl.

4. Step IV – Hydrolysis: A water molecule, activated by His41, attacks the thioester carbonyl, generating a second tetrahedral intermediate.

5. Step V – Product release: Collapse of these intermediate regenerates the free cysteine thiol and releases the C-terminal peptide product (R–COOH), completing the catalytic cycle.

Nirmatrelvir binds the active site of 3 $C^{pro}$ , blocking viral proce.

As shown in the Figure 4, Ritonavir does not directly act on SARS-CoV-2 proteases. At low doses co-administered for the strong inhibition of cytochrome P450 3A4 (CYP3A4), it acts as a pharmacokinetic booster, reducing the metabolic clearance of nirmatrelvir to achieve plasma

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concentrations in excess of the inhibitory limit for the dosing interval, enhancing the antiviral activity [13].

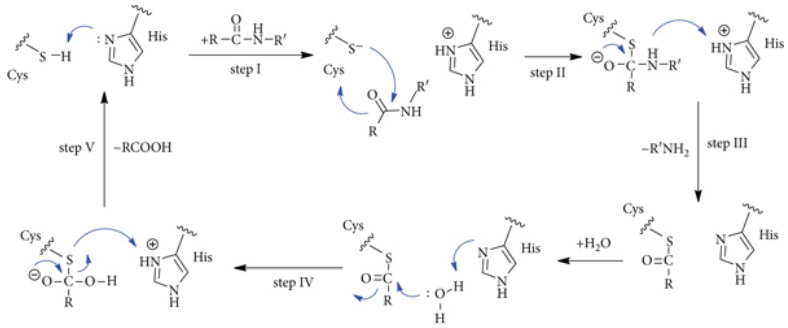



Figure 4. Representation of the 3C$L^{pro}$-mediated catalytic cleavage mechanism of coronavirus polyproteins [6]

### 5.3. Pharmacokinetics and drug–drug interactions

It must also be noted that the addition of ritonavir mandates proper consideration of pharmacokinetic interactions, since ritonavir's powerful CYP3A4 inhibition can cause clinically important interactions with numerous frequently used drugs, including statins, some anticoagulants, antiarrhythmics, immunosuppressants, and many others. The consensus clinical guidance files recommend prior to prescribing Paxlovid, reconciliation of patient medication, de-prescribing or dose reduction of comorbid drugs, and, where indicated, specialist advice [13]. Such potential drug–drug interactions have been the major practical deterrent to the successful deployment of Paxlovid's high inherent antiviral activity.

### 5.4. Clinical performance and limitations

Paxlovid has been reported consistently in both clinical trials and subsequent real-world studies to clearly impact progression to severe disease and hospitalization in high-risk, non-hospitalized patients when administered early in the disease course [2]. In meta-analytic comparisons, Paxlovid appears to be somewhat superior in preventing severe outcomes in a comparable target population to molnupiravir [9]. But the utility of Paxlovid may also be limited by its drug–drug interactions, by shortage in some environments, and by a need for alternative agents like molnupiravir when Paxlovid is contraindicated or unavailable

## 6. Comparative analysis and clinical decision making

### 6.1. Mechanism-driven strengths and vulnerabilities

Molnupiravir's mechanism—lethal mutagenesis via RdRp incorporation—confers broad antiviral potential and a lower propensity for direct drug–drug interactions, because it does not rely on CYP-mediated pharmacokinetic boosting [7]. However, its mechanism raises specific safety questions [10], and its clinical potency appears lower than Paxlovid's in head-to-head aggregated analyses [9]. The protease inhibitor (Paxlovid) effectively directly inhibits an essential viral enzymatic activity, exhibits strong clinical efficacy, and has the downside of interactions with ritonavir and the necessity of medication adherence [13].

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### 6.2. Clinical selection framework

Clinicians selecting an agent should take into consideration:(1) timing of treatment initiation—each agent is especially efficacious if administered within as short a time as possible after symptom onset; (2) patient comorbidities and background medications—Paxlovid may be contraindicated, or its use may be more complex in patients taking highly critical interacting medication; (3) pregnancy and reproductive concerns—Molnupiravir's mutagenic mode of action may prompt caution in some populations. (4) drug access and local rules [2,9]. In several health systems, eligible patients are treated first with Paxlovid and reserved Molnupiravir for when Paxlovid is contraindicated and/or not available.

### 6.3. Public health and access considerations

Beyond individual patient selection, equitable access to oral antivirals is a public-health priority. Manufacturing scale, distribution logistics, cost, and intellectual property issues influence availability across regions. While this review focuses on mechanism and clinical evidence, policy makers should integrate these clinical insights into allocation frameworks that optimize population-level benefit [4].

## 7. Future directions and research priorities

Important issues for the future involve (1) Molnupiravir long-term safety (in terms of host genotoxicity and cancer risk) [10].(2) the sustained effectiveness of Paxlovid's activity against new variants that carry possible protease mutations (i.e. surveillance needs to be carried out); (3) the effectiveness of combination treatments or sequential approaches in minimizing resistance risk; (4) the effect of initiating antiviral therapy in the early stages of treatment and the subsequent incidence of long COVID (i.e. prospective cohort studies need to be carried out) [2,9]. Large-scale real-world effectiveness analyses and mechanistic studies together with longer follow-up for safety endpoints will be necessary in order to further shape therapeutic recommendations.

## 8. Conclusion

Molnupiravir and Paxlovid are two clinically useful, mechanistically distinct oral antiviral strategies for the outpatient treatment of COVID-19. Molnupiravir causes lethal mutagenesis of the viral genome through RdRp incorporation and has a broad antiviral utility with relatively reduced drug–drug interactions but poses certain specific safety concerns. Paxlovid delivers robust inhibition of a conserved viral protease and strong clinical efficacy early, but calls for careful medication reconciliation because of ritonavir's CYP3A4 inhibition. Clinical selection should be individualized, balancing efficacy, interaction risk, contraindications, and availability. Ongoing pharmacovigilance and comparative effectiveness research will be key to optimizing its use and ensuring patient safety.

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