

## The Biological Activity and Synthesis of Orally Active COVID-19 (SARS-CoV-2) Antiviral Drug Molnupiravir

Tanmoy Sahoo<sup>a,b</sup>, Priyanka Shrivastava<sup>c</sup>, Anirban Chandra<sup>d</sup>, Swapan Kumar Biswas<sup>d\*</sup> and B. V. Subba Reddy<sup>a\*</sup>

**Keywords:** SARS-CoV-2, Antiviral, Cytidine, Uridine, D-Ribose Molnupiravir, Ribonucleoside.

### Abstract:

In the midst of the COVID-19 pandemic, a multitude of potential drugs have emerged, among them molnupiravir (MK-4482 and EIDD-2801), an innovative oral antiviral designed to combat COVID-19. Currently undergoing final clinical trials, molnupiravir has displayed encouraging results in boosting the replication process of viral RNA mutations in both animal and human subjects. With the urgent demand for its production, it became an urgent need for the society to establish an efficient and feasible synthetic pathway from basic materials. This research delves into the molecular docking analysis of molnupiravir, shedding light on its mechanism of action (MOA) while outlining the most recent synthetic processes. Such insights are poised to benefit various disciplines, including medicinal chemistry, organic chemistry, biochemistry, and pharmacology. Marketed under the brand name Lagevrio, molnupiravir stands out as a simple yet potent orally active antiviral medication. Initially developed for treating influenza, its application has expanded to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has an exceptional potency as the first oral, direct-acting antiviral medication against SARS-CoV-2. This review explores different synthetic strategies/routes employed in the synthesis of molnupiravir, with the aim of facilitating the development of novel routes for its further enhancement.

### Introduction:

The COVID-19 pandemic, stemming from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, has presented a significant global health challenge. As of

---

#### Tanmoy Sahoo<sup>a,b</sup>

<sup>a</sup>Fluoro-Agrochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India

<sup>b</sup>Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002, India

Orcid iD: <https://orcid.org/0009-0008-5483-7136>

#### Priyanka Shrivastava<sup>c</sup>

<sup>c</sup>Holy Cross School, Durjoynagar, Airport Road, Agartala, 799006, Tripura(West), India

Orcid iD: <https://orcid.org/0009-0009-5545-6084>

#### Anirban Chandra<sup>d</sup>

Department of Chemistry, Tripura University, Suryamaninagar, 799022, Tripura(West), India

Orcid iD: <https://orcid.org/0009-0009-8943-9530>

#### Swapan Kumar Biswas<sup>d\*</sup>

<sup>d</sup>Department of Chemistry, Tripura University, Suryamaninagar, 799022, Tripura(West), India

E-mail: [swapankumarbiswas@tripurauniv.ac.in](mailto:swapankumarbiswas@tripurauniv.ac.in); Orcid iD: <https://orcid.org/0000-0002-2757-7702>

#### B. V. Subba Reddy<sup>a\*</sup>

<sup>a</sup>Fluoro-Agrochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India

E-mail: [basireddy@iict.res.in](mailto:basireddy@iict.res.in); Orcid iD: <https://orcid.org/0000-0003-0814-583X>

\*Corresponding Author: [swapankumarbiswas@tripurauniv.ac.in](mailto:swapankumarbiswas@tripurauniv.ac.in) & [basireddy@iict.res.in](mailto:basireddy@iict.res.in)

March 8<sup>th</sup>, 2021, over 115 million individuals had been infected, with nearly 2.5 million fatalities worldwide (Aleccia et.al, 2021; Roychoudhury et.al, 2021; Kalal & Charola, 2021; Vashist et. al, 2023). In the midst of this crisis, molnupiravir emerges as a promising treatment option. Originally conceived as an antiviral medication for influenza, this prodrug features a nucleoside scaffold of N4-hydroxycytidine (Halford et.al, 2020, Hu et.al, 2021). Initially developed at Emory University in collaboration with the university's drug innovation ventures at Emroy, it is now being advanced by Merck as a novel oral antiviral agent for combating COVID-19 (Chavda et.al, 2023). Animal studies have showcased molnupiravir's effectiveness in preventing viral transmission and inhibiting SARS-CoV-2 (Chavda et.al, 2022). Operating as an oral antiviral ribonucleoside analog, molnupiravir is regarded as a 5'-isobutyrate prodrug of the direct-acting antiviral ribonucleoside analog, EIDD-1931, or  $\beta$ -D-N4-hydroxycytidine. Upon entry into the bloodstream, molnupiravir undergoes cleavage to release EIDD-1931. Within cells, EIDD-1931 undergoes phosphorylation by host kinases to form its active antiviral form, the corresponding 5'-triphosphate (Bian et.al, 2022, Maurya et.al, 2022)

### Biological Activity

In animal models infected with various coronaviruses, influenza virus, and the Ebola virus, EIDD-1931 has demonstrated successful inhibition of replication across multiple RNA viruses (Akkiz et.al, 2021, Abu-Zaied et.al, 2021). This orally administered drug exhibits high potency against SARS-CoV-2 infection, with a favorable safety profile (Sezer et.al, 2022). Phase 1 clinical trials have shown that molnupiravir, as a novel oral antiviral medication, is well tolerated and safe for healthy volunteers (Gil et.al, 2020). In Phase 2 trials involving patients with mild to moderate COVID-19, the drug was administered twice daily for five days in a placebo-controlled, double-blind, randomized, multicenter trial. Results indicated a reduction in SARS-CoV-2 transcription process, cleansing of infectious virus, prevention of COVID-19 progression, and successful inhibition of SARS-CoV-2 replication (Sezer et.al, 2022, Gil et.al, 2020, Sharma et.al, 2021). Findings from the Phase 2/3 trial were presented at the European Congress of Clinical Microbiology and Infection Disease (ECCMID), demonstrating promising outcomes for non-hospitalized COVID-19 patients (Khan et.al, 2020). Merck and Ridgeback Bio are collaborating to develop a new antiviral compound, EIDD-2801. This review mainly focuses on the drug's action mechanism and the new synthetic pathway of molnupiravir as an antiviral agent, aiming to illuminate the rational synthesis of more effective molnupiravir variants as potential antiviral candidates.

Molnupiravir was developed by Emory University as part of an antiviral drug screening project funded by the Defense Threat Reduction Agency (DTRE). This initiative aimed to combat the Venezuelan equine encephalitis virus (VEEV) (Aleccia et.al, 2021). Specifically, EIDD-2801 is a prodrug effective against different RNA viruses like influenza, Ebola, chikungunya, and various coronaviruses. In 2019, the National Institute of Allergy and Infectious Diseases (NIAID) sanctioned molnupiravir for Phase I clinical trials targeting influenza (Halford et.al, 2020).

Subsequently, amidst the COVID-19 pandemic in 2020, Ridgeback Biotherapeutics acquired the drug in collaboration with Merck & Co., USA. During the COVID-19 pandemic, human health and the social economy were severely affected worldwide. Globally, more than 767 million COVID-19 cases have been reported according to the WHO. Structural changes through mutation of SARS-CoV-2 have affected its transmissibility, therapeutic agent effectiveness, disease severity, and ultimately human health (Abu-Zaied et.al, 2021). Due to the high mutation rate of SARS-CoV-2 virus, any type of therapy against this virus as become challenging, leading to the repurposing of several antiviral agents to treat COVID-19 patients (Fischer et.al, 2022). Among these developments, orally active molnupiravir has demonstrated robust anti-SARS-CoV-2 activity in both in vitro and in vivo trials (Teli et.al, 2023). Importantly, it has also shown efficacy against the Omicron variant of SARS-CoV-2 (Rautio et.al, 2018).

Molnupiravir is an isopropyl pro-drug of N-hydroxycytidine. Prodrugs are biologically inactive substances that are biotransformed by the body into pharmacologically active compounds (Hacker et.al, 2009, Jornada et.al, 2016). They play an important role in designing and discovery of new drug in medicinal chemistry (Markovic et.al, 2020, Painter et.al, 2021). In many cases, scientists engineered the prodrugs to improve the bioavailability of the drug, and molnupiravir has been specifically formulated to address the low bioavailability of N-hydroxycytidine (Toots et.al, 2019, Yoon et.al, 2028, *Int. J. Stroke* 2018). Research has investigated the uptake and distribution of N-hydroxycytidine in mice (Kabinger et.al, 2021). Molnupiravir, on the other hand, has been observed to impede the transcription and replication of the viral RNA genome of coronaviruses by targeting the RNA-dependent RNA polymerase (RdRp), thereby inducing copying errors (Gordon et.al, 2021, Yip et.al, 2022, Toots et.al, 2020). Initially, the prodrug molnupiravir undergoes activation by the host cell enzyme (carboxyl esterase) to generate the N-hydroxycytidine compound, which is biologically active one (Painter et.al, 2019, Wang et.al, 2022), which is then subsequently converted to N4-hydroxycytidine triphosphate by host cell kinases (Painter et.al, 2019). Thenafter it targets the RdRp, which is virally encoded, and the RdRp uses the NHC triphosphate as a substrate instead of cytidine and uridine triphosphates, inhibiting viral replication (**Fig 1**). Due to its significant benefits, this drug has attracted immense interest among scientists to develop an efficient, sustainable and cost-effective synthetic route for its production. This chapter of the book comprehensively outlines various synthetic methodologies for the synthesis of molnupiravir, elucidating the strengths and limitations of each approach.

### Molnupiravir Metabolism:

Originally developed for influenza treatment in 2019, molnupiravir acts as an oral prodrug of N6-hydroxycytidine. However, with the emergence of SARS-CoV-2, molnupiravir has exhibited strong anti-SARS-CoV-2 activity both in vitro and in animal models. Numerous nucleosides and analog nucleotides have been identified as potential target and selective antiviral inhibitors of coronaviruses, including SARS-CoV-2, showcasing a wide spectrum range of antiviral activity.

Some of these compounds have swiftly progressed into clinical trials for COVID-19 treatment (Fig. 2). Unlike other COVID-19 drugs granted emergency use authorization (EUA), molnupiravir can be produced on a larger scale.

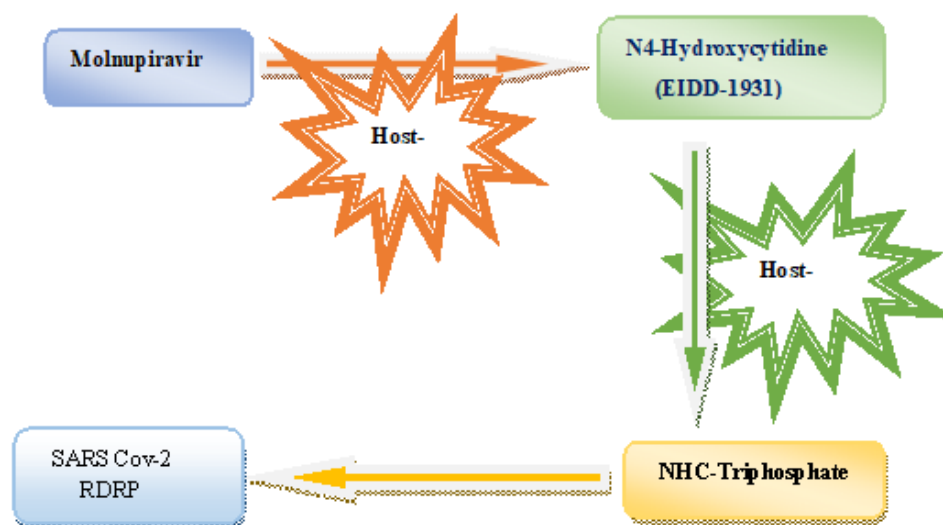


Fig.1 Schematic diagram of N4-hydroxycytidine triphosphate

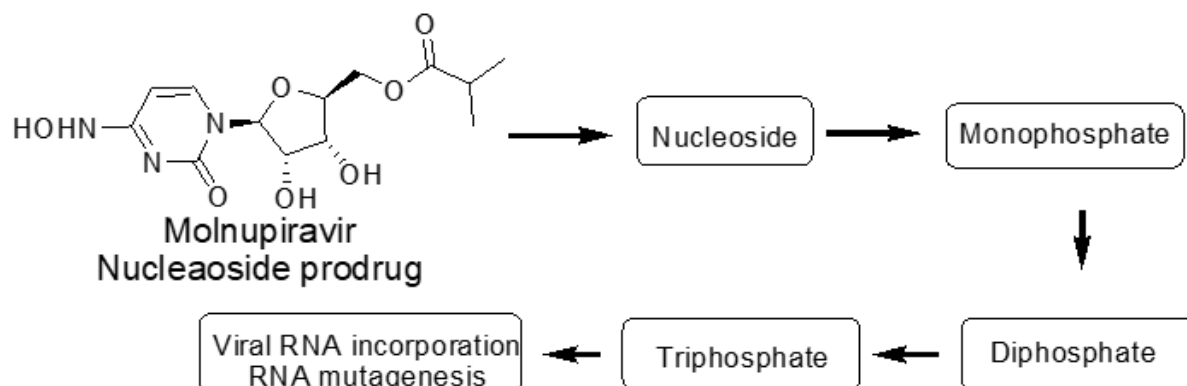


Fig. 2 Structure of nucleoside analog of molnupiravir and its metabolic activation.

Furthermore, this drug does not necessitate in-hospital settings or cold transportation for administration. Evidence from phase 1, 2, and 3 clinical trials has indicated that molnupiravir is better tolerated and safer in the short term, without any significant side effects (Teli et.al, 2023).

### Mechanism of action of molnupiravir

Since the coronavirus pandemic began, a number of research projects have been initiated to investigate ways to combat the new novel virus. Researchers have been diligently developing various vaccines and drug moieties, each with differing degrees of success. Molnupiravir,

initially designed to combat influenza, emerged as another potential candidate for antiviral treatment. Understanding the molecular mechanistic pathway of molnupiravir is crucial for advancing the development of antiviral drugs.

Upon metabolism within the body, molnupiravir becomes an RNA-like component once it enters the cell. Initially, RNA polymerase (the viral copy machine) incorporates these components into the RNA genome of the virus. Subsequently, RNA-like components pair with viral genetic material components. As viral RNA multiplies to generate new viruses, it accumulates several mutations, thereby impeding pathogen reproduction. This antiviral drug induces mutations in other RNA viruses, thereby halting their expansion.

Molnupiravir, the promising drug, currently undergoing phase 3 studies, exhibits a unique mechanism of action. Once inside the cell, molnupiravir is converted into its active form, N-hydroxycytidine hydrate (NHC triphosphate or MTP). Interestingly, the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 can replace MTP with cytidine triphosphate (CTP) or uridine triphosphate (UTP) (Fig. 2A). Particularly during the synthesis of sub-genomic RNA and negative-strand genomic RNA using positive-strand genomic RNA as a template, RdRp consistently substitutes M for U or C. Subsequently, +gRNA or +sgmRNA (positive-strand sub-genomic mRNA) can be derived from RNA containing M as a template. As a result of this process, mutations occur in the positive-stranded genomic RNA products, stemming from the incorporation of M in negative-strand genomic RNA (Fig. 2B). Consequently, this impedes the formation of new viable viruses. In conclusion, this two-step mechanism illustrates how molnupiravir and its activated form induce RNA mutations through the polymerases of other viruses (**Fig. 3**).

Previous studies have shown that molnupiravir-induced lethal mutagenesis is facilitated by the relatively high selectivity of N-hydroxycytidine triphosphate (MTP) for incorporation as a cytidine triphosphate (CTP) analog. Moreover, the indiscriminate incorporation of either adenosine triphosphate (ATP) or guanosine triphosphate (GTP) takes place when molnupiravir monophosphate (MNP) is concentrated in the template strand, indicating at least a two-step mechanism. The initiation of Cytosine to uracil mutations could occur downstream of the erroneously incorporated AMP (Adenosine Monophosphate) and uridine triphosphate (UTP) incorporation could subsequently occur. The replication fidelity necessary for viability is delineated by the accumulation of mutations that exceed the viral replication "error threshold." In conclusion, molnupiravir exhibits favorable pharmacokinetic characteristics, making it highly suitable for oral delivery (Painter et.al, 2021).

### **Dose and safety of molnupiravir in patients infected with the coronavirus**

Agile is a Phase Ib/IIa platform designed for the swift evaluation of COVID-19 therapies. In a study led by Khoo, Saye H., *et al.* [16] (registered as NCT04746183), the safety and optimal dosage of molnupiravir in combating primary SARS-CoV-2 infection were assessed. Participants were randomly assigned to receive oral doses of 300 mg, 600 mg, or 800 mg of molnupiravir

twice daily for five consecutive days. If the likelihood of dose-limiting toxicity exceeding 30% was greater than 25%, it was deemed unsafe. Secondary outcomes included clinical improvement, safety, virological responses, and pharmacokinetics. From July 17<sup>th</sup> to October 30<sup>th</sup>, 2020, a study enrolled eighteen participants out of 103 screened. The results demonstrated that molnupiravir was well-tolerated at doses of 300 mg, 600 mg, and 800 mg, with no severe adverse effects observed. Overall, molnupiravir demonstrated safety and good tolerability in the second phase of assessment, leading to the recommendation of administering a dose of 800 mg twice daily for five consecutive days.

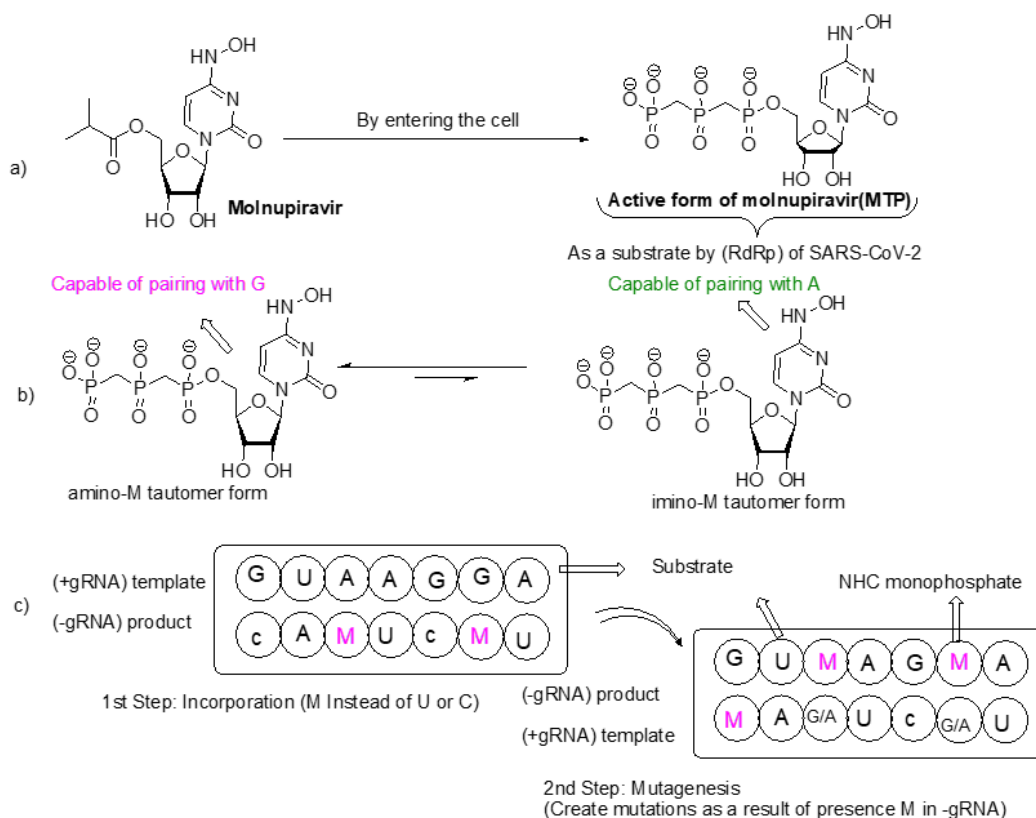


Fig. 3 Mechanism of action of molnupiravir.

The conversion of molnupiravir drug to its active form in the cell involves several steps. Initially, molnupiravir is metabolized to N-hydroxycytidine (NHC) within the cell. Subsequently, NHC undergoes phosphorylation by host cell kinases to form NHC monophosphate (MNP). Further phosphorylation of MNP yields NHC diphosphate (MNP), which finally gets converted to NHC triphosphate (MTP), the active form of molnupiravir, capable of inhibiting viral RNA replication.

NHC triphosphate (MTP) can exist in different tautomeric forms, including the hydroxylamine form (2) and the oxime form (3). The hydroxylamine form allows MTP to pair with guanosine

(G) and function similarly to cytidine (C). On the other hand, the oxime form enables MTP to pair with adenosine (A) and function like uridine (U).

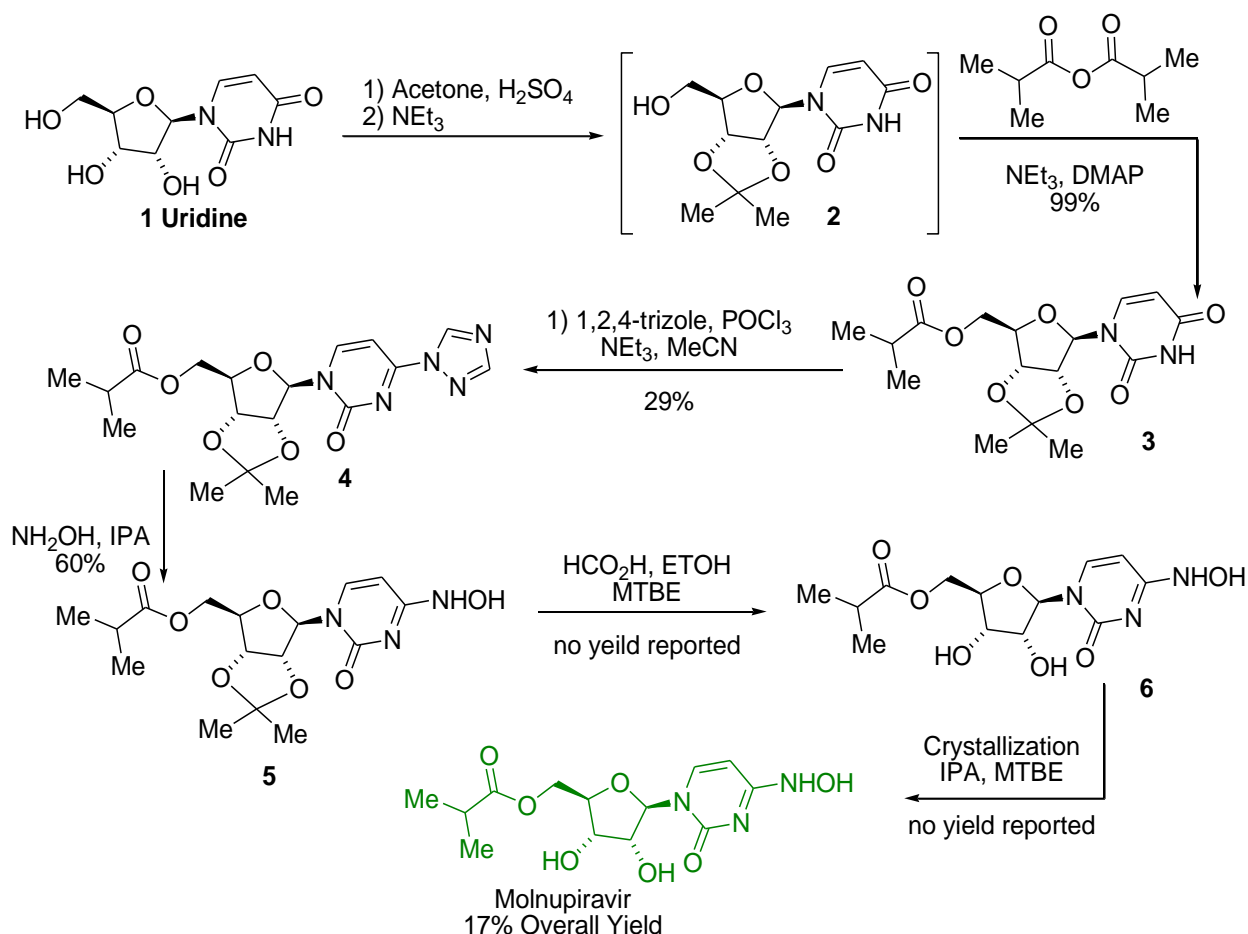
A two-step model is used to explain Molnupiravir-induced RNA mutagenesis. In the first step, the RNA-dependent RNA polymerase (RdRp) substitutes NHC (M) for uridine (U) or cytidine (C) during RNA synthesis from positive-strand genomic RNA (+gRNA). In the subsequent stage, mutations arise in positive-stranded genomic RNA products as a result of the presence of NHC (M) in negative-strand genomic RNA, thereby impeding viral replication.

### SYNTHETIC ROUTES TO ACCESS THE MOLNUPIRAVIR:

Emory University unveiled the primary synthesis route for molnupiravir (Yoon et.al, 2018). Following this pathway, molnupiravir undergoes five sequential steps, initiating from uridine (4). While the yield of the final two steps remains unreported in this study, the overall synthetic process attains a maximum yield of 17%. Initially, the vicinal diol undergoes protection using acetone and sulfuric acid at room temperature for 18 h to yield acetonide (5). After purification by trimethylamine, 4-(N, N-dimethylamino) pyridine (DMAP), and triethylamine (Et<sub>3</sub>N), the reaction mixture is cooled to 0 °C, followed by gradual addition of isobutyric acid anhydride (6) and subsequent warming to room temperature.

Acetonitrile solution of compound (3) is then added to the reaction mixture containing triethylamine and 1,2,4-triazole. Upon cooling, phosphoryl chloride (POCl<sub>3</sub>) is introduced, and the solution is warmed to room temperature, yielding the corresponding triazole (4). Compound (5) is obtained by treating 2-Propanol (2-PrOH) solution of compound (4) with hydroxylamine (NH<sub>2</sub>OH) at r.t, yielding 60%. Using neat formic acid, deprotection is performed at room temperature, yielding molnupiravir (10), which is finally crystallized and recrystallized using 2-PrOH/MTBE (**Scheme 1**).

Vasudevan, N. (Vasudevan et.al, 2020) group proposed a very short pathway for molnupiravir synthesis, which involve esterification, followed by hydroxyamination of cytidine. This approach achieves a yield of 75%, a substantial upliftment over the previously reported 17%. The number of steps is also reduced from five to two, and the expensive uridine is replaced by cytidine. With minor modifications to the reaction conditions, N(4)-hydroxycytidine (NHC) is synthesized with a yield of 70%. Notably, pure NHC is obtained directly from the reaction mixture with a 50% isolated yield through simple crystallization after concentration, thus circumventing dihydroxyamination with NH<sub>2</sub>OH\_H<sub>2</sub>SO<sub>4</sub> in <sup>t</sup>PrOH when investigating transamination of cytidine isobutyryl ester. The synthesis of molnupiravir achieves a high yield from the compound, highlighting the feasibility of direct hydroxyamination from both cytidine reaction pathways, which drops to 37% when hydroxyamination is performed (**Scheme 2**).



**Scheme 1: Synthetic pathway revealed from molnupiravir by Emory University in 2019.**

Synthesizing Molnupiravir is quite challenging, particularly its purification, despite being its structural simplicity, a prodrug composed of N-hydroxycytidine and ribose. In the last couple of years, various research teams globally have devised multiple synthetic pathways using uridine, cytidine, or ribose as the primary starting materials.

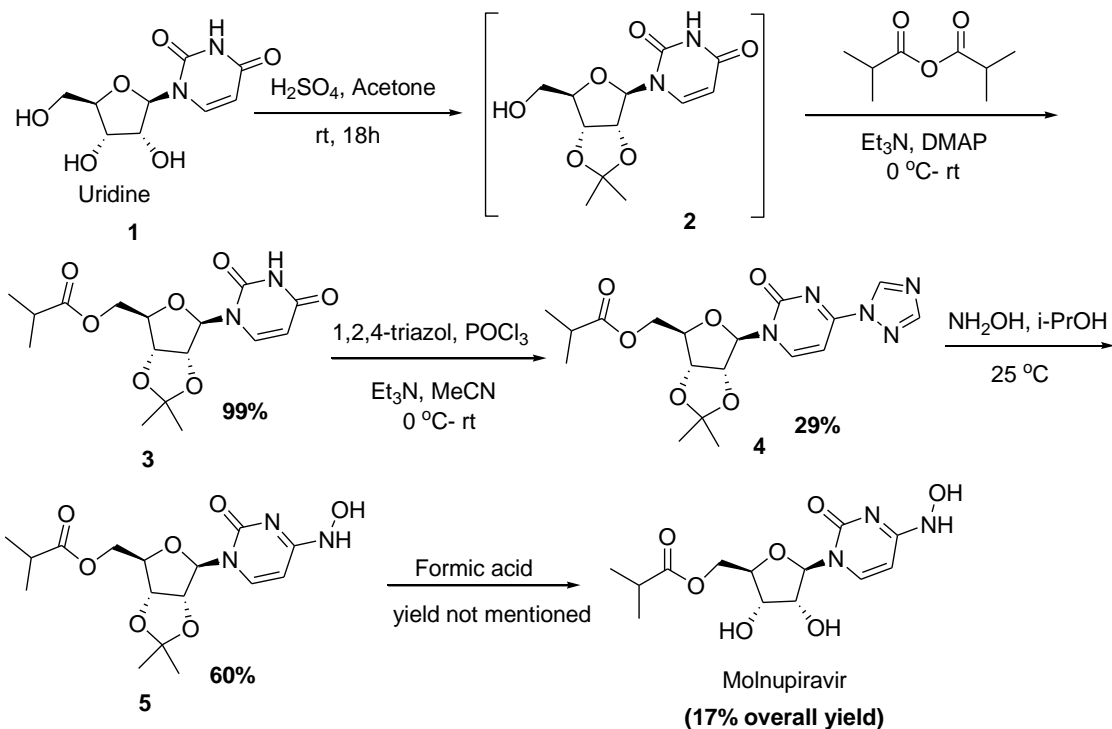
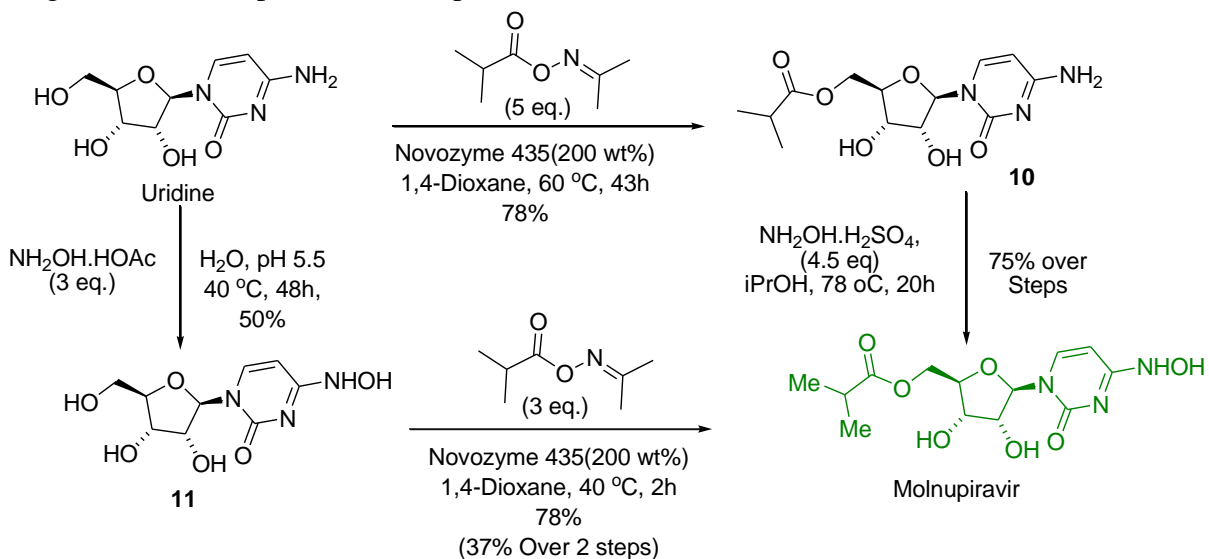
### Synthesis from Uridine (a natural nucleoside):

Amarante *et al.* reported the synthesis of Molnupiravir, with the first synthetic route disclosed by Emory University in 2019. This route involves five synthetic transformations starting from uridine, yielding Molnupiravir in 17% yield (Amarante *et al.* 2022). (**Scheme 3**).

The initial step in this process involves the formation of the isobutyl ester **3** protection of uridine as its acetonide, followed by esterification using isobutyric anhydride in the presence of triethylamine, with almost cent percent yield. Following this, compound **3** undergoes treatment with excess 1,2,4-triazole and phosphorus oxychloride in the presence of a base ( $\text{Et}_3\text{N}$ ), resulting in the triazole derivative **4** with a yield of 29%. Subsequently, the nucleophilic substitution of **4** by hydroxylamine hydrochloride in isopropanol yields the N-hydroxycytidine derivative **5** with



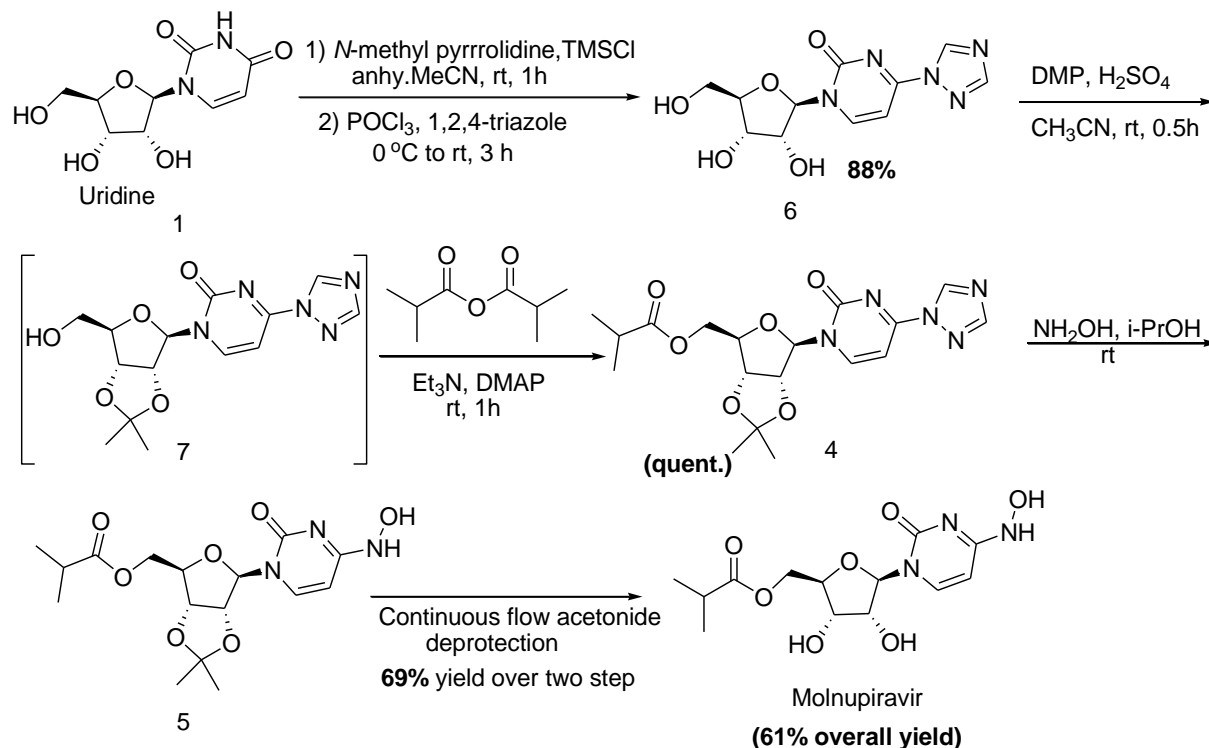
moderate yield (~60%). This compound **5** is then subjected to the deprotection of the acetonide using formic acid to produce Molnupiravir.



However, this method suffers from a low overall yield after five consecutive steps (17%) and requires excess triazole. These factors limit its applicability in large-scale synthesis.

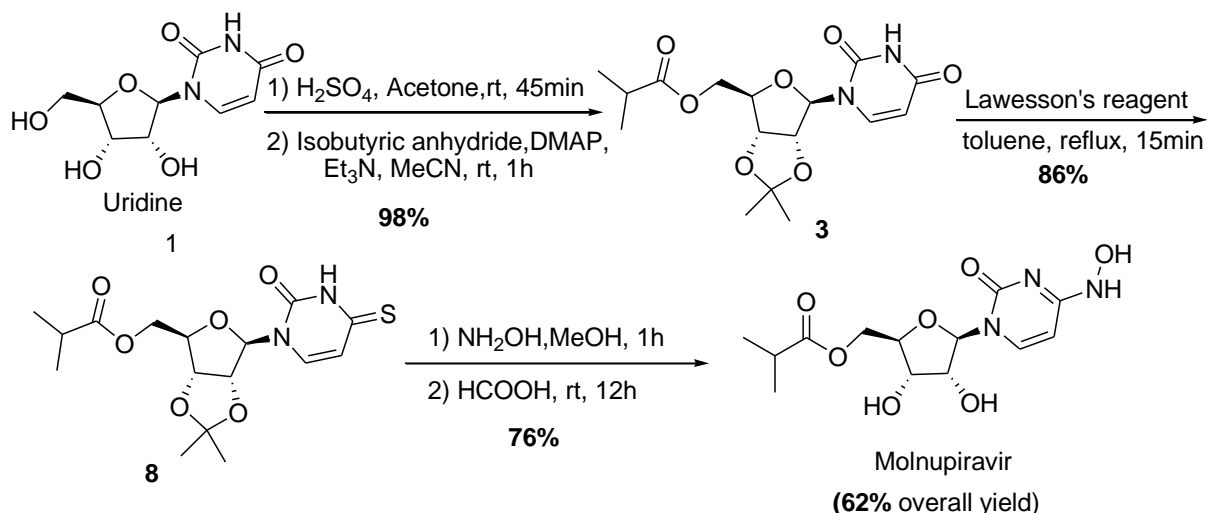
In 2020, Kappe *et al.* (Steiner *et al.* 2020) introduced an enhanced synthetic route for Molnupiravir (**Scheme 4**). Initially, triazolization of uridine was conducted, yielding an 88% yield, followed by acetonide protection/esterification, resulting in the formation of triazolyl uridine **4**

in quantitative yield. Subsequently, hydroxyamination and acetonide deprotection of compound **4** were carried out under continuous flow conditions, leading to the production of the final compound Molnupiravir with a 69% yield. Despite the overall yield improvement from 17% to 61%, one drawback of this process is the requirement for excess triazole.



**Scheme 4: Improved synthetic route by Kappe *et al.***

In 2021, Das *et al.* (Dey *et al.* 2021) introduced a novel pathway for Molnupiravir synthesis (**Scheme 5**) [33]. This method entails a one-pot synthesis: acetonide protection followed by uridine esterification, yielding compound **3** in a 98% yield. Subsequently, it is converted into thiouridine **8**, a key intermediate in this process, with an 86% yield in the presence of Lawesson's reagent. Thiouridine **8** is then transformed into the final compound Molnupiravir through a one-pot synthetic process, hydroxyamination followed by acetonide deprotection and the route delivers the product with a 62% overall yield and >99% purity, although it necessitates a stoichiometric quantity of Lawesson's reagent.



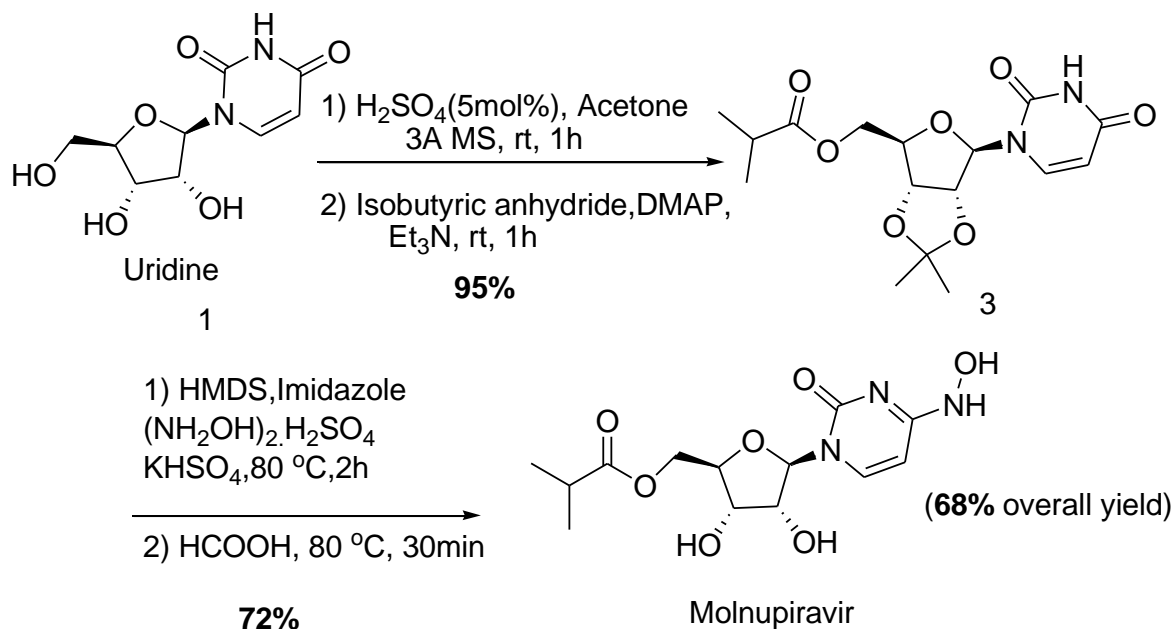
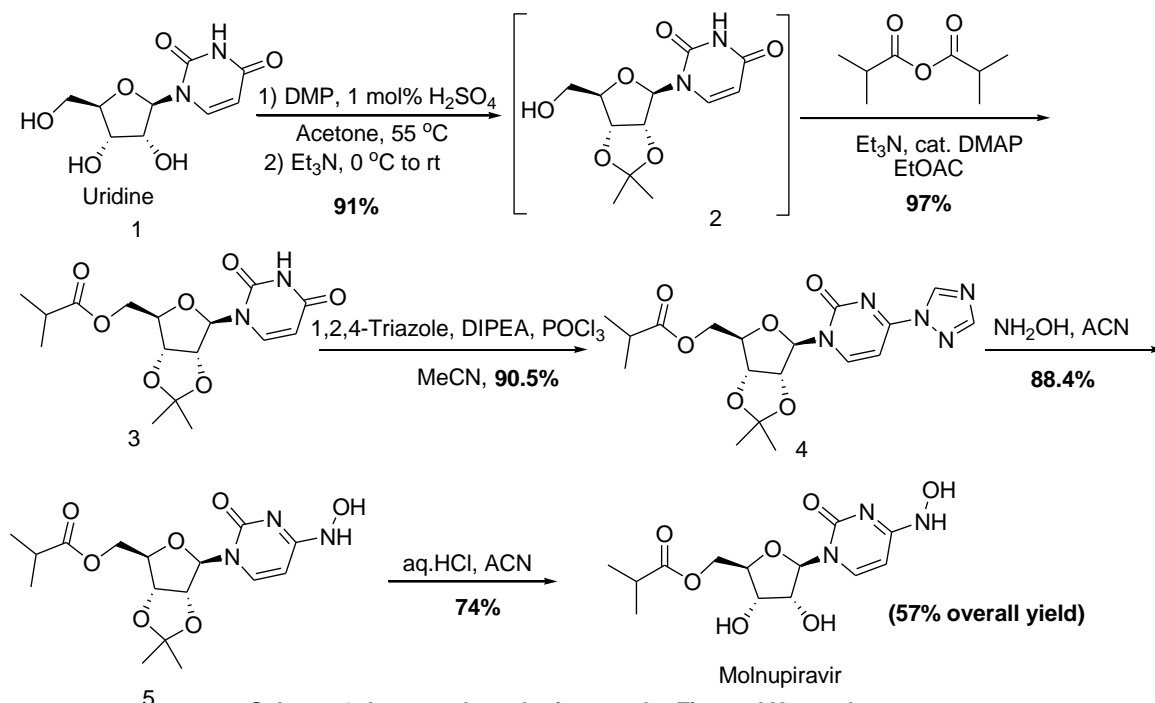
#### Scheme 5: Novel synthetic route of molnupiravir through thiouridine intermediate

In 2021, Fier *et al.* (Fier *et al.* 2021) presented an enhanced synthetic process for Molnupiravir (**Scheme 6**). They achieved a 1.6-fold increase in overall yield by enhancing the yield in each synthetic step of the original synthetic route as disclosed by Emory University. The synthesis was started with the protection of uridine under the condition of 1 mol% of  $\text{H}_2\text{SO}_4/\text{DMP}$  in acetone at  $55^\circ\text{C}$ . Quenching the reaction mixture with  $\text{Et}_3\text{N}$  yielded compound 2, with the yield better by 1.3-fold compared to the original process.

Subsequently, treatment of compound 2 with isobutyric anhydride,  $\text{Et}_3\text{N}$ , and catalytic DMAP in ethyl acetate, providing compound 3 in a 97% yield. Triazolization of compound 3 was achieved with a 90.5% yield by treating it with 1,2,4-triazole, DIPEA, and  $\text{POCl}_3$  in acetonitrile. Hydroxylamination was then carried out using  $\text{NH}_2\text{OH}$  (50 wt% in  $\text{H}_2\text{O}$ ) in acetonitrile, followed by acetonide deprotection in the presence of aqueous  $\text{HCl}$  to yield Molnupiravir with a 57% overall yield.

In 2022, De Souza *et al.* (Pereira *et al.* 2022) devised a concise two-step synthetic route for Molnupiravir (**Scheme 7**). Regarded as one of the most efficient synthetic processes, this method employed product purification through pH-controlled extraction, followed by crystallization. A one-pot synthesis initiated with acetonide protection and esterification of uridine under established reaction conditions, with subsequent purification achieved through pH-controlled extraction, yielding a 95% yield.

The subsequent step involved the hydroxylamination of compound 3, accomplished by treating hydroxylamine sulfate with HMDS in the presence of imidazole and  $\text{KHSO}_4$ . Acetonide deprotection was then achieved using formic acid at  $80^\circ\text{C}$ , resulting in the production of Molnupiravir with a 68% overall yield.

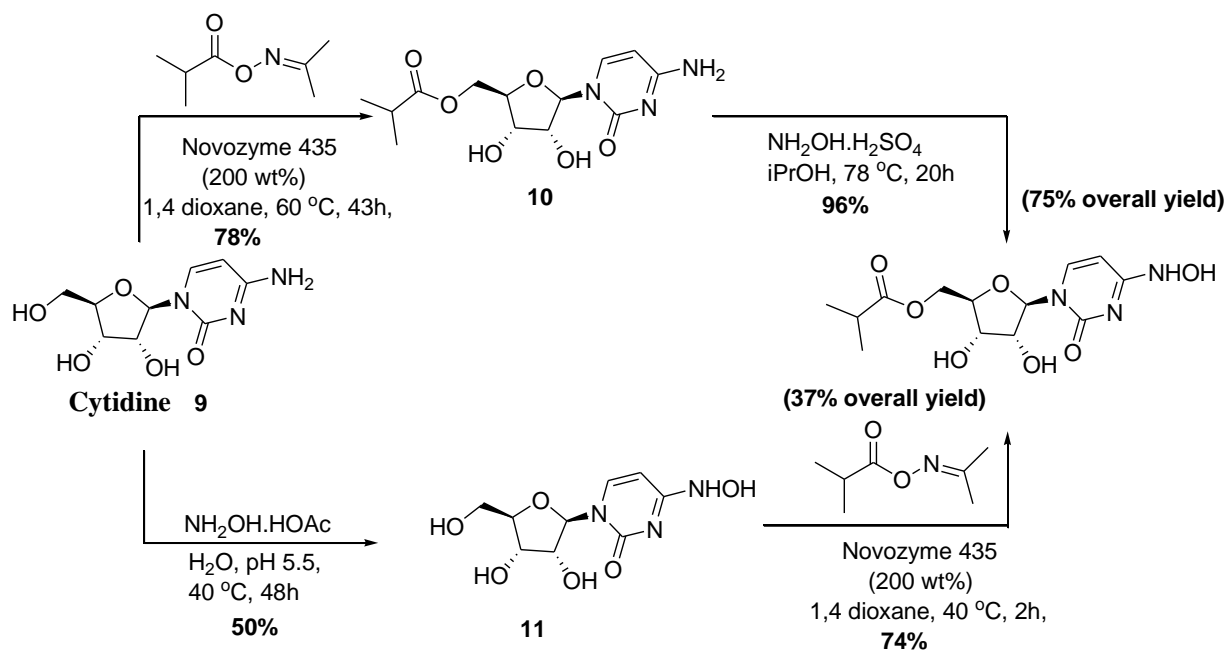


### Synthesis of Molnupiravir using Cytidine as the starting material:

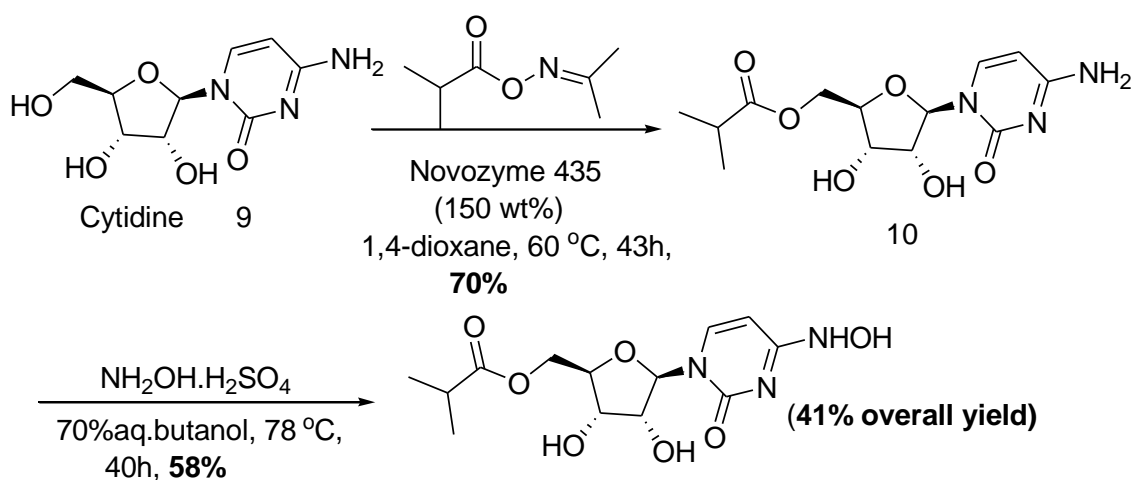
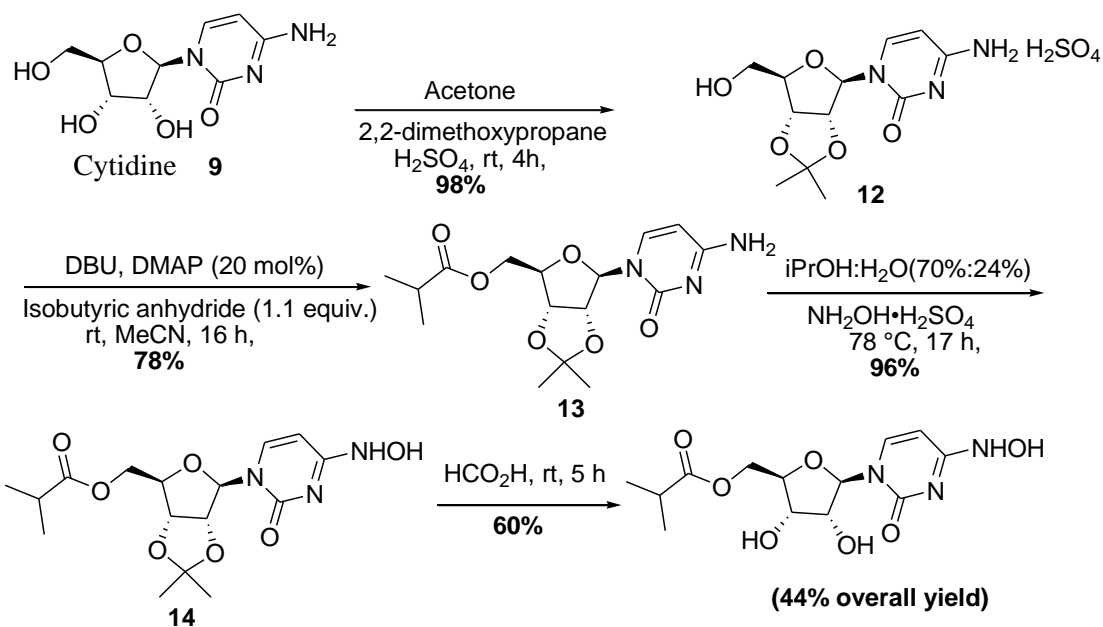
Various research groups have documented the synthesis of Molnupiravir using uridine as a primary starting material. However, scientists have also explored an alternative approach by synthesizing Molnupiravir from a more readily available and cheap starting material, cytidine.

In 2020, Gopalsamuthiram *et al.* introduced a novel and succinct route for synthesizing Molnupiravir from cytidine (**Scheme 8**) (Gopalsamuthiram *et al.* 2020), employing two distinct synthetic pathways.

In the first route, Novaenzyme-435 (200 wt%) facilitated the cytidine's selective esterification, yielding the mono-ester **10** with an impressive 78% yield. Subsequently, hydroxyamination of compound **10** was done in the presence of hydroxylamine sulfate, resulting in the formation of Molnupiravir with an outstanding 96% yield, thus achieving a 75% overall yield. Conversely, in the second route, hydroxyamination was conducted as the initial step, followed by esterification, yielding Molnupiravir with a 37% overall yield. This method offers a significant advancement by substituting the expensive uridine starting material with the more cost-effective and readily available cytidine.

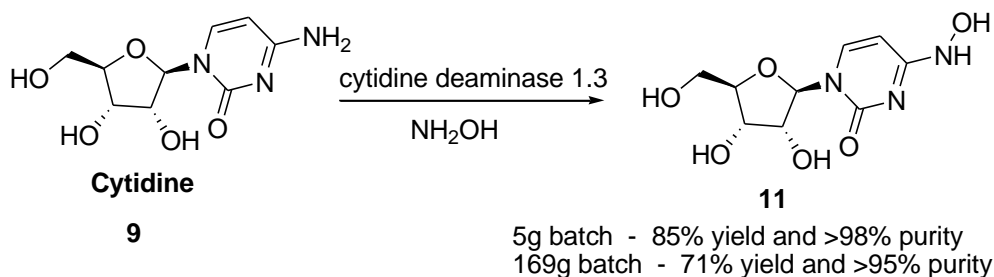


In the same year, Jamison *et al.* developed a non-enzymatic synthetic route for Molnupiravir from cytidine. The protection of dihydroxyl group of cytidines was carried out in the presence of 2,2-dimethoxypropane and catalytic sulfuric acid in acetone, yielding a 98% yield. Subsequently, non-enzymatic acylation with isobutyric anhydride, DBU, and catalytic DMAP is performed. Hydroxyamination and deprotection of the acetonide are performed under formic acid condition, resulting in the formation of Molnupiravir (**Scheme 9**) (Ahlqvist *et al.* 2021). Utilizing low-cost reagents, the overall process was conducted to produce Molnupiravir, achieving an overall yield of 44%.



Bruke *et al.* designed a two-step synthetic approach for synthesizing Molnupiravir on a large scale from cytidine (**Scheme 10**) (Bruke *et al.* 2022). This method involves enzymatic acylation of cytidine with Novozyme 435 (150 wt%) to yield the desired product in 78% yield. Subsequently, hydroxyamination is carried out in the presence of hydroxylamine sulfate, resulting in a 58% yield. Notably, column purification is not necessary at any point in the process. Despite the relatively low overall yield of around 41%, this method offers a significant advantage for large-scale synthesis (up to 200g) due to the absence of column purification, streamlining the manufacturing process.

Turner *et al.* introduced a method for the biocatalytic production of a crucial intermediate **11**, of Molnupiravir (**Scheme 11**) (Hu *et al.* 2022). In this process, the synthetic conversion from cytidine to N-hydroxy cytidine was facilitated by an engineered variant of cytidine deaminase (CD1.3) enzyme. This variant exhibits a preference for hydroxyaminolysis over the hydrolysis of cytidine. Notably, the desired product is produced with good yield and excellent purity through this innovative enzymatic process, even at high substrate concentrations. Furthermore, the product underwent purification via crystallization. Consequently, this method shows significant potential as a cost-effective approach for the synthesis of Molnupiravir.

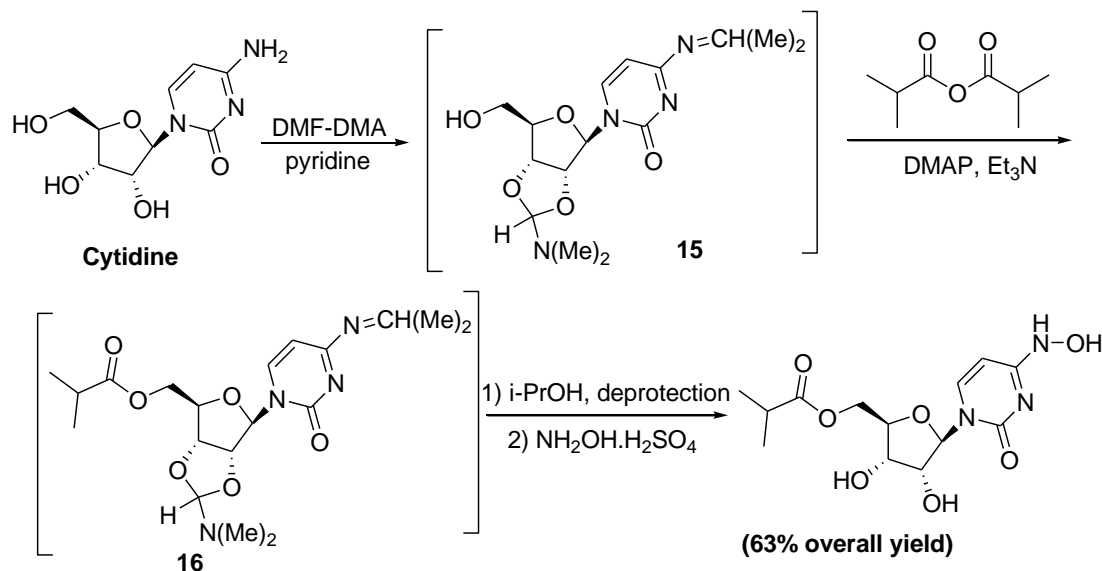


**Scheme 11: Enzymatic synthesis of N-hydroxy cytidine key intermediate by Turner *et al.***

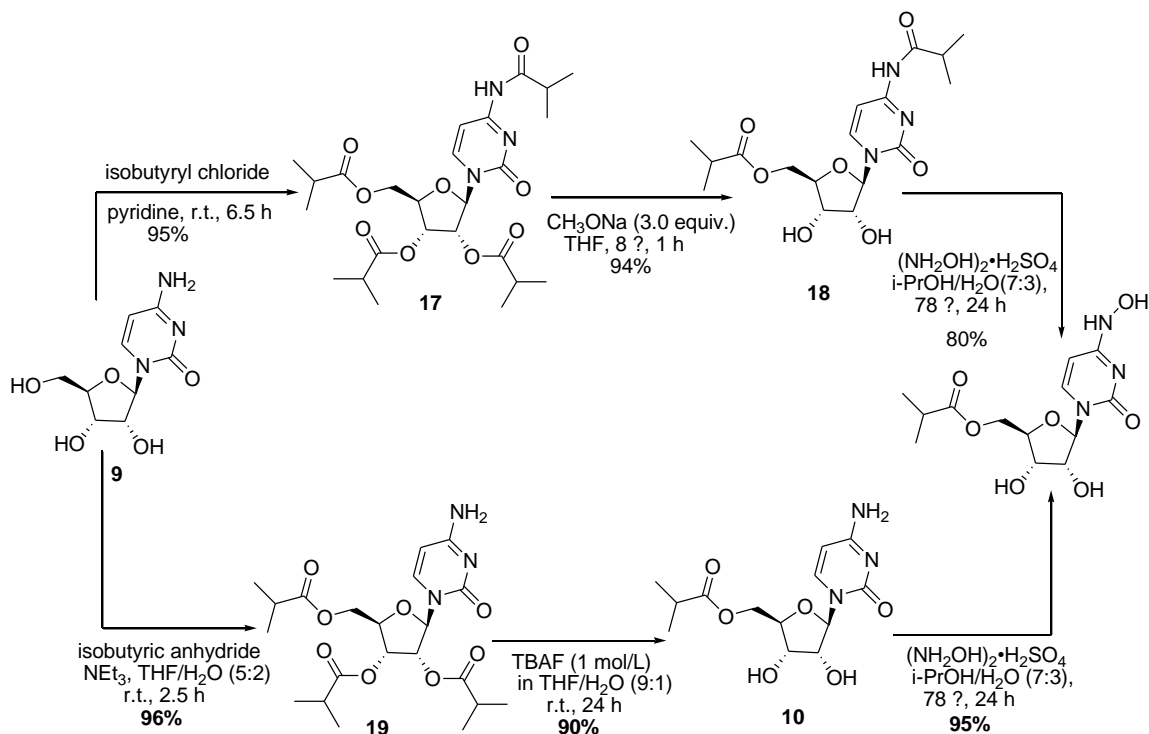
Aisa *et al.* devised a streamlined one-pot synthetic process to produce Molnupiravir from cytidine, achieving an impressive yield of 70% (Scheme 12) [40]. The synthesis initiates with the protection of cytidine's 2° OH group and 1° amine group utilizing DMF-DMA reagent in the presence of 10 equivalents of pyridine in THF solvent, yielding crude compound 15. Subsequently, this compound is subjected to a series of transformations: treatment with isobutyric anhydride, Et<sub>3</sub>N, and catalytic DMAP in DCM solvent at room temperature, resulting in the formation of ester 16. Following this, ester 16 undergoes further reaction with <sup>i</sup>PrOH and a mixture of 70% <sup>i</sup>PrOH/water, along with hydroxylamine sulfate, under heating conditions at 78°C for 18 hours. Upon cooling to room temperature, the organic layer is concentrated to dryness, and the crude Molnupiravir is then crystallized from 2-methyltetrahydrofuran, followed by re-slurry in 2-PrOAc. This comprehensive process yields Molnupiravir with an overall yield of 63%. Notably, the method's single-step isolation and utilization of a highly labile protecting group contribute significantly to minimizing yield loss. These features render Aisa *et al.*'s method highly efficient and promising for large-scale Molnupiravir synthesis.

Liu *et al.* proposed a three-step non-enzymatic synthetic method for accessing Molnupiravir (**Scheme 13**) (Liu *et al.* 2022). The synthesis of Molnupiravir initiates with cytidine, which undergoes conversion into compound **17** with a remarkable yield of 95% using isobutyric anhydride. Following this, selective deprotection of compound **17** employing sodium methoxide furnishes compound **18** in a high yield of 94%. Subsequently, hydroxyamination of compound **18** yields the target Molnupiravir with an impressive yield of 80%. Overall, this synthetic pathway achieves a remarkable 71% overall yield, underscoring its efficiency and potential for large-scale production. In an alternative approach, they have been capable of growth the general

yield to 82% via tri-acylation in place of tetra-acylation of cytidine (**19**), followed by selective deprotection and hydroxylamination.



**Scheme 12: One-pot synthetic route to molnupiravir by Aisa *et al.***

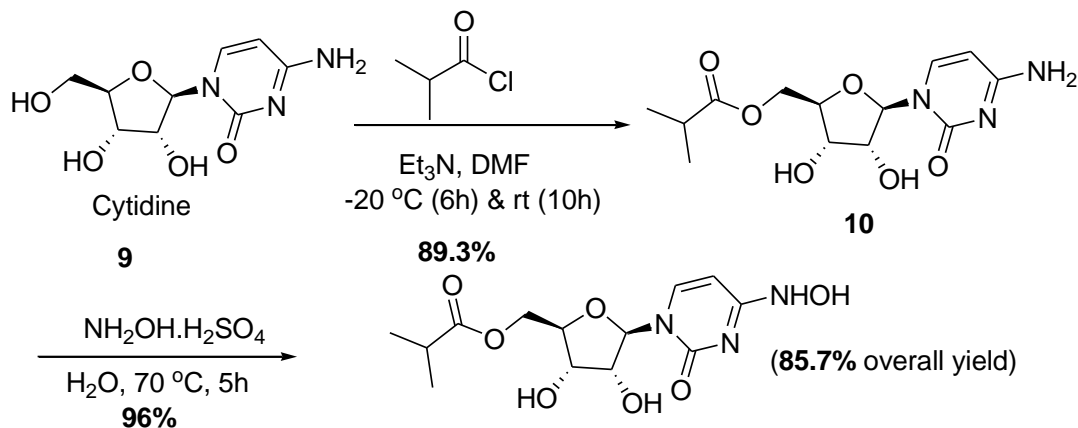


**Scheme 13: Three steps synthetic route by F. Liu *et al.***

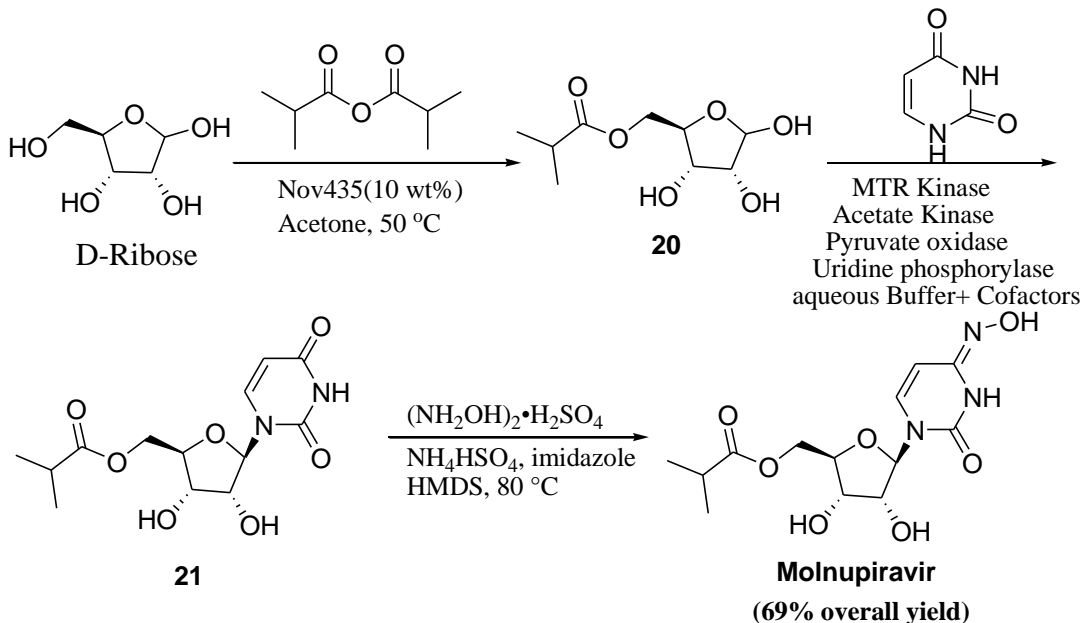
A two-step chemical synthesis has been carried out by Venkatanarayana *et al.* 2023, group using cytidine as the starting material which is commercially available and inexpensive (**Scheme 14**). The first step contains selective Acylation of Cytidine without Enzyme in DMF with



Isobutyryl Chloride and  $\text{Et}_3\text{N}$ , yielding compound **10** with 89.3% yield. This step is considered one of the novel key steps in this process. Subsequently, compound **10** is treated with hydroxylamine sulfate in  $\text{H}_2\text{O}$  at  $70^\circ\text{C}$  for 5 hours to obtain the final compound Molnupiravir in a remarkable 96% yield. This approach utilizes low cost commercially available supplies and concise steps, offering potential for exploring the synthesis of Molnupiravir on a larger scale.



**Scheme 14: Two steps synthetic route by P. Venkatanarayana *et al.***

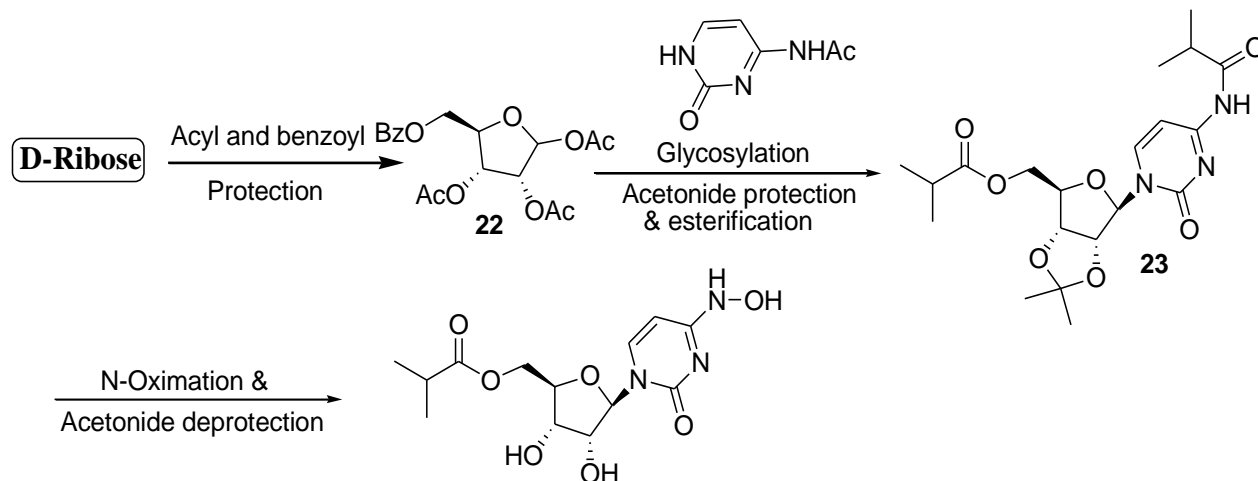


**Scheme 15: Enzymatic synthesis of Molnupiravir from Ribose**

### Synthesis from D-Ribose:

Ribose emerges as one of the most economical key starting materials when compared to cytidine and uridine. However, only a handful of methods have been documented for synthesizing Molnupiravir using D-Ribose as the starting material. In 2020, Benkovics *et al.* presented an efficient three-step enzymatic route for Molnupiravir synthesis (**Scheme 15**). The initial step of this process entails the selective esterification of D-ribose utilizing the Novazyme-435

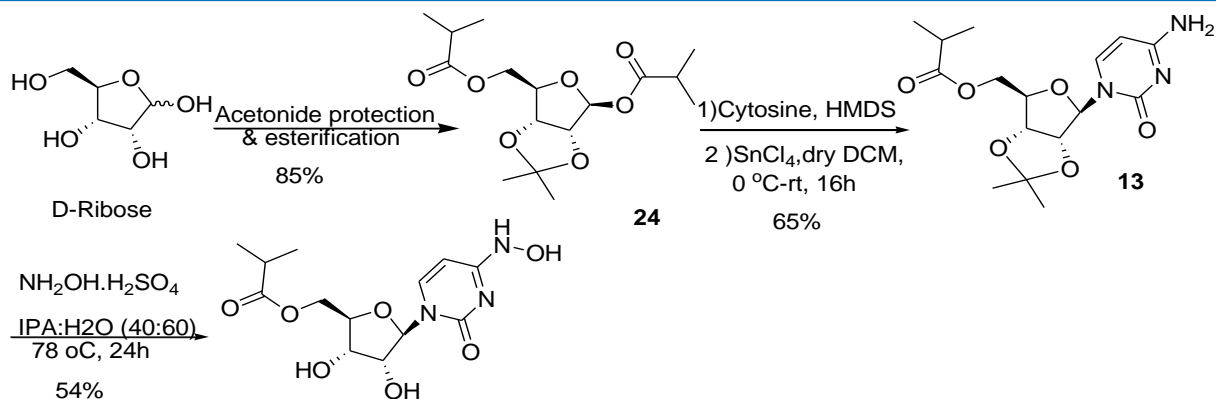
biocatalyst, resulting in an impressive yield of 94%. Subsequently, 1-phosphorylation followed by coupling with uracil using acetate kinase leads to the formation of compound **21**. Compound **21** is then converted into Molnupiravir by hydroxyamination in the presence of HMDS. Despite starting from commodity chemicals like ribose and uracil, the major limitation of this process lies in the non-commercial availability of the enzymes used.



**Scheme 16: A convenient synthetic approach to Molnupiravir (EIDD-2801) from Ribose**

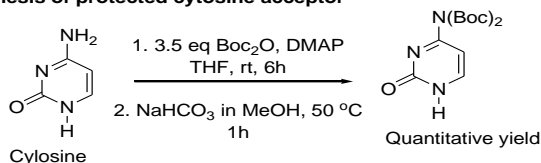
An appropriate/suitable synthesis method for Molnupiravir was provided by Mukherjee *et al.* by the conversion of N-acyl amidines to amidoximes (**Scheme 16**) (Ahmed et al. 2021). The synthesis initiates with the protection of ribose to yield acetate **22**, followed by coupling with N-acetyl cytosine. Subsequent acetonide protection and esterification result in the formation of nucleoside **23**. Hydroxyamination followed by acetonide deprotection of compound **23** yields Molnupiravir in a 62% overall yield. While this methodology yields satisfactory overall results, it necessitates numerous chemical transformations such as protection and deprotection during the process, adding complexity to the synthesis.

In 2022, Reddy's research group innovated a concise three-step chemical process aimed at accessing Molnupiravir from readily available D-Ribose (Sahoo et al. 2022). This strategic approach aimed to streamline the synthesis while ensuring efficiency and scalability. The process commenced with the selective esterification of D-Ribose, leveraging optimized reaction conditions to achieve a high yield. Subsequently, the intermediate underwent a series of carefully orchestrated transformations, each designed to introduce key functional groups essential for Molnupiravir synthesis. Finally, purification steps were implemented to enhance the purity of the final product, ensuring compliance with rigorous quality standards. This innovative methodology not only offers a more efficient route to Molnupiravir but also holds promise for large-scale production, contributing to the accessibility and affordability of this crucial antiviral drug.

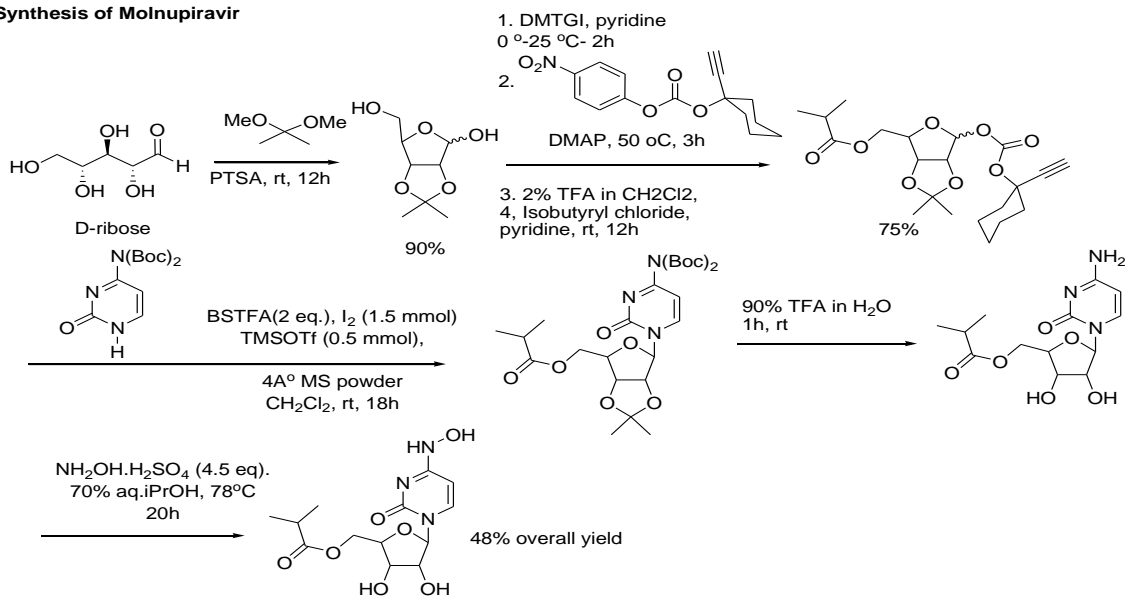


**Scheme 17: Concise three steps chemical process to access the Molnupiravir**

**Synthesis of protected cytosine acceptor**



**Synthesis of Molnupiravir**

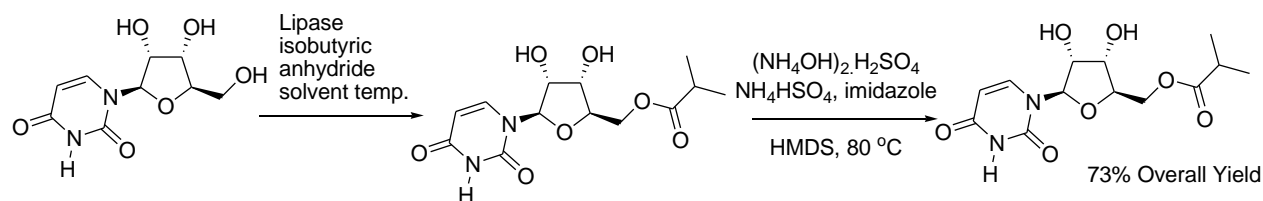


**Scheme 18: Synthesis of Molnupiravir from D-Ribose and Cytosine**

Chakraborty *et al.* 2024, synthesized glycosyl donor 5 from D-ribose (**Scheme 18**) [46], initially attempting anomeric allyl protection but shifting to acetonide group protection due to yield loss from ribopyranoside formation. Ribofuranoside 7 was obtained in 90% yield. Donor 5 was synthesized in 75% overall yield after three sequential reactions, including primary hydroxyl group protection, conversion to ethynyl cyclohexyl propargyl donor, DMT group cleavage, and esterification with isobutryl chloride. Cytosine's amine group was protected with bis-Boc group. N-glycosylation reactions with donor 5 resulted in mainly O-glycosidic product formation, with less than 20% N-glycosidic product. Optimization revealed AgOTf as the cocatalyst and TMSOTf as the additive, yielding up to 90% glycosylation yield. Using I2 and TMSOTf, the

nucleosidation reaction produced the desired  $\beta$  isomer **8** in 90% yield, with gram-scale compatibility. After removing Boc and acetonide groups, hydroxylation at the N4 position yielded Molnupiravir.

Bade *et al.* presented a synthesis pathway for Molnupiravir (**Scheme 19**) [47], starting with intermediate synthesized from uridine under optimized conditions using lipase Addzyme 011 (TLL) and isobutyric anhydride in THF at 40 °C for 96 hours, demonstrating excellent regioselectivity at the primary alcohol. Subsequently, the amidic carbonyl of uracil in intermediate **2** was converted to an oxime using cost-effective hexamethyldisilazane (HMDS) as the solvent and mild dehydrating agent, with imidazole serving as a catalyst to enhance conversion rates via TMS-imidazole formation. This approach contrasts with Merck and Co.'s enzymatic process utilizing ribose, achieving a 69% overall yield, and Hu *et al.* and Ahlqvist *et al.*'s one-pot chemical synthesis from cytidine, yielding 63% overall. These methods involved protection and deprotection steps or a chemo-enzymatic process utilizing Novozyme 435, resulting in a 41% overall yield, albeit limited by expensive substrates and relatively poor yields. In order to overcome these obstacles, Bade *et al.*'s research target was to use inexpensive uridine and reducing the number of steps, while achieving good overall yields in the synthesis of molecular Molnupiravir.

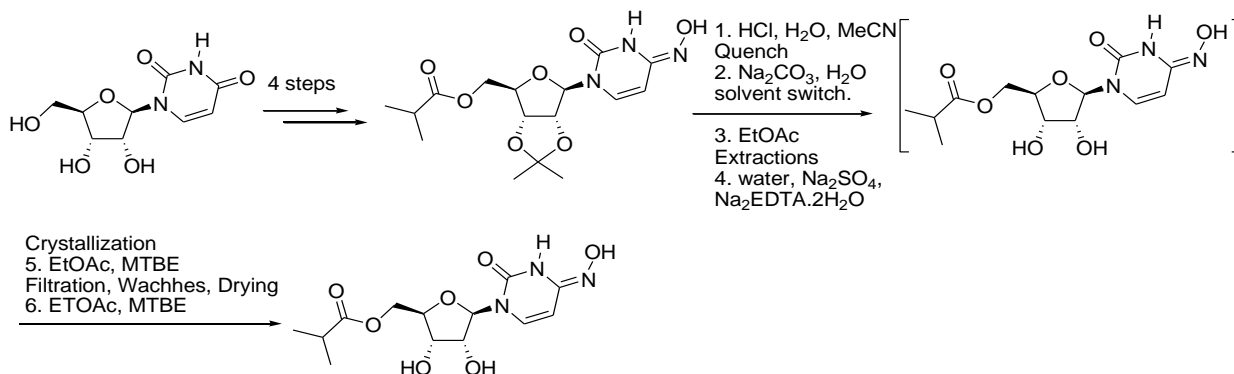


**Scheme 19: Chemo-Enzymatic Synthesis of Molnupiravir via Lipase**

Rachel *et al.* conducted stability studies on molnupiravir Forms 1 and 2, (**Scheme 20**) [48] both as drug substance and in formulated capsules. They found no significant changes in impurity profile or physical attributes over 6 months at accelerated conditions, indicating stability at intended storage conditions. Drug product stability tests showed consistent crystal forms and no significant changes in key properties like chemical stability and dissolution. No hydrate formation was observed. Both forms exhibited stability over 3 months in bottles and open dish conditions at elevated humidity and temperature. XRPD confirmed no change in crystal form, demonstrating similarity and suitability for pharmaceutical use.

Furthermore, stability assessments of the drug product were performed to assess the influence of crystal form on various attributes, including chemical stability and dissolution. Following the formulation of Molnupiravir Form 1 and Form 2 into capsules via a high-shear wet granulation process, it was observed that the original crystal form persisted consistently in the final product. As Molnupiravir does not form hydrates, hydrate formation was not considered a concern during the drug production process or in stability testing under elevated relative humidity.

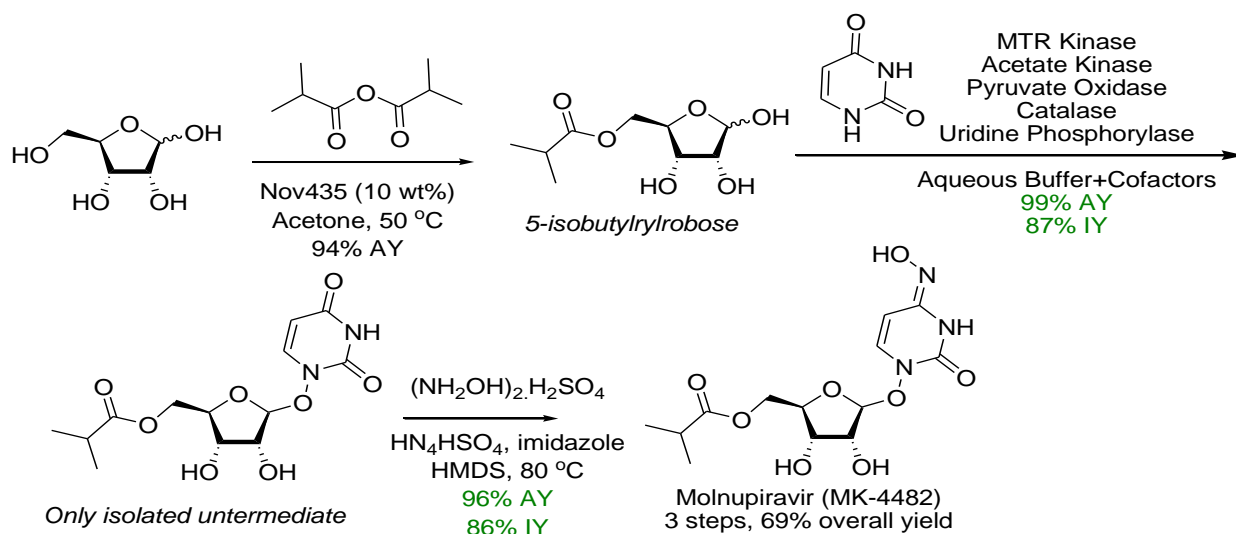
Drug product capsules containing either Form 1 or predominantly Form 2 drug substances were subjected to accelerated stability conditions (40°C/75% RH) for up to 3 months, both in bottles and in open dish conditions. The resulting stability data for both Form 1 and Form 2 indicated no notable changes observed in key drug product properties, including chemical stability and dissolution profile. Additionally, X-ray powder diffraction (XRPD) analysis confirmed the retention of Molnupiravir's crystal form throughout the drug product stability testing.



**Scheme 20:** Schematic of the abbreviated manufacturing process for molnupiravir.

At the same time, we focused on making a reliable manufacturing process to always make the Active Pharmaceutical Ingredient (API) of the same quality. At first, we isolated the API using distillative crystallization. In this process, a solution with API, EtOAc, MeCN, and water is distilled, and dry EtOAc is added to make the water content lower, which makes the API form crystals because it's very soluble in water. We improved this method to have better control over when crystals start forming and how quickly they grow. This made the API more consistent in quality across different batches and scales. Even though this updated process was a bit more complex to run, we chose it because it was more reliable, especially with tight project deadlines and concerns about regulatory approval for any changes in the Particle Size Distribution (PSD) or crystal form.

In 2021, the McIntosh *et al.* (**Scheme 21**) group emphasized Molnupiravir (MK-4482) as a promising investigational antiviral agent for treating COVID-19. Recognizing the likely high demand and urgent need for this compound, it became imperative to establish a concise and sustainable synthesis route using readily available raw materials to expedite the manufacturing and distribution of Molnupiravir. The approach presented in their study relies on a groundbreaking biocatalytic cascade, featuring an engineered ribosyl-1-kinase and uridine phosphorylase. These engineered enzymes are coupled with a phosphate recycling strategy enabled by pyruvate oxidase. In comparison to the initial synthetic route, this new method for producing Molnupiravir is 70% shorter and yields around seven times higher. Looking ahead, the biocatalytic tactic outlined for Molnupiravir synthesis is expected to find widespread use in simplifying the production of nucleosides across various applications.



**Scheme 21: Ribosyl-1-Kinase Enables Concise Synthesis of Molnupiravir**

In summary, various approaches have been explored for the synthesis of Molnupiravir from its three primary starting materials (*e.g.* uridine, cytidine and ribose), offering potential avenues for discovering new routes for large-scale production at an affordable price. While numerous research groups have dedicated considerable time and effort to investigating the synthesis of this drug, a comparative analysis reveals that only a few routes exist for synthesizing Molnupiravir from ribose. Moreover, the enzymatic pathway for obtaining Molnupiravir from ribose is not the most favoured option due to the lack of commercially available enzymes. Nevertheless, we believe that this review could serve as a valuable resource for the scientific community, particularly in furthering the development of Molnupiravir from ribose, given its natural availability and cost-effectiveness as a precursor.

## Acknowledgments

T. Sahoo thanks to CSIR, New Delhi, India, for the award of a fellowship and Indian Institute of Chemical Technology-Hyderabad (CSIR-IICT) and Dr. A. Chandra and Dr. S K. Biswas thanks to VC Tripura University and HOD Chemistry, Tripura University and Tripura University.

## References:

- Abu-Zaied, M. A.; Elgemeie, G. H.; Mahmoud, N. M. Anti-covid-19 drug analogues: synthesis of novel pyrimidine thioglycosides as antiviral agents against SARS-COV-2 and avian influenza H5N1 viruses. *ACS Omega* **2021**, *6*(26), 16890–16904. doi.org/10.1021/acsomega.1c01501.
- Ahlqvist, G. P.; McGeough, C. P.; Senanayake, C.; Armstrong, J. D.; Yadaw, A.; Roy, S.; Ahmad, S.; Snead, D. R.; Jamison, T. F. Progress Toward a Large-Scale Synthesis of Molnupiravir (MK-4482, EIDD-2801) from Cytidine. *ACS Omega* **2021**, *6*, 10396-10402. doi.org/10.1021/acsomega.1c00772.
- Ahmed, A.; Ahmed, Q. N.; Mukherjee, D. Conversion of *N*-acyl amidines to amidoximes: a convenient synthetic approach to molnupiravir (EIDD-2801) from ribose. *RSC Adv.* **2021**, *11*, 36143-36147. doi.org/10.1039/D1RA06912H.

- Akkiz, H. Implications of the Novel Mutations in the SARS-CoV-2 Genome for Transmission, Disease Severity and the Vaccine Development. *J. Transl. Sci.* 2021, 7, 636532. DOI: 10.3389/fmed.2021.636532.
- Aleccia, J. (29 September 2021). "A Daily pill to treat COVID could be just months away". *ABC News*. Kaiser Health News. Archived from the original on 29 September 2021.
- Bade, R., Bothe, J. R., Sirota, E., Brunskill, A. P. J.; Newman, J. A., Zhang, Y., Tan, M., Zheng, M., Brito, G., Poirier, M., Fier, P. S., Xu, Y., Ward, M. D., Stone, K., Lee, I. H., Gmitter, A. J., Bernardoni, F., Zompa, M. A., Luo, H. Patel., S. K., Masiuk, T., Mora, J., Ni, T., O., G. A.; Tarabokija, J., Liu, J., Lowinger, M. B.; Mahmood, T., Polymorphs, Particle Size, and a Pandemic: Development of a Scalable Crystallization Process for Molnupiravir, an Antiviral for the Treatment of COVID-19, *Org. Process Res. Dev.* 2023, 27, 11, 2100–2110. doi.org/10.1021/acs.oprd.3c00268.
- Benkovics, T.; McIntosh, J.; Silverman, S.; Kong, J.; Maligres, P.; Itoh, T.; Yang, H.; Huffman, M.; Verma, D.; Pan, W.; Ho, H.I.; Vroom, J.; Knight, A.; Hurtak, J.; Morris, W.; Strotman, N.; Murphy, G.; Maloney, K.; Fier, P. Evolving to an ideal synthesis of Molnupiravir, an investigational treatment for COVID-19. *ChemRxiv*. 2020. 10.26434/chemrxiv.13472373.v1.
- Bian, L.; Gao, F.; Zhang, J.; He, Q.; Mao, Q.; Xu, M.; Liang, Z. Effects of SARS-CoV-2, Variants on Vaccine Efficacy and Response Strategies. *Expert Rev. Vaccines* 2021, 20, 365–373. DOI: 10.1080/14760584.2021.1903879.
- Burke, A. J.; Birmingham, W. R.; Zhuo, Y.; Thorpe, T. W.; da Costa, B. Z.; Crawshaw, R.; Rowles, I.; Finnigan, J. D.; Young, C.; Holgate, G. M.; Muldowney, M. P.; Charnock, S. J.; Lovelock, S. L.; Turner, N. J.; Green, A. P. An Engineered Cytidine Deaminase for Biocatalytic Production of a Key Intermediate of the Covid-19 Antiviral Molnupiravir. *J. Am. Chem. Soc.* 2022, 144, 3761–3765. DOI: 10.1021/jacs.1c11048
- Chakraborty S, Sutar Y, Prasad K, Rajput J, Hotha S. Expedient Synthesis of Antiviral Drug Molnupiravir from D-Ribose and Cytosine. *ChemRxiv*. 2024; doi:10.26434/chemrxiv-2024-gd0tn.
- Chavda, V.P.; Balar, P.; Vaghela, D.; Solanki, H.K.; Vaishnav, A.; Hala, V.; Vora, L. Omicron Variant of SARS-CoV-2: An Indian Perspective of Vaccination and Management. *Vaccines* 2023, 11, 160. Pati, B.; Banerjee, S. "Quinazolines: an illustrated review, *J. Adv. Pharm. Edu. Res.*, 2013, 3, 136–151. doi.org/10.3390/vaccines11010160.
- Chavda, V.P.; Yao, Q.; Vora, L.K.; Apostolopoulos, V.; Patel, C.A.; Bezbaruah, R.; Patel, A.B.; Chen, Z.-S. Fast-Track Development of Vaccines for SARS-CoV-2: The Shots That Saved the World. *Front. Immunol.* 2022, 13, 961198., WHO Coronavirus (COVID-19) Dashboard, <https://covid19.who.int/>, accessed 2023. DOI: 10.3389/fimmu.2022.961198.
- Dey, R.; Nayak, S.; Das, P.; Yadav, S. Short Synthesis of Molnupiravir (EIDD-2801) via a Thionated Uridine Intermediate. *ACS Omega* 2021, 6, 28366–28372. DOI: 10.1021/acsomega.1c04550.
- Fier, P. S.; Xu, Y.; Poirier, M.; Brito, G.; Zheng, M.; Bade, R.; Sirota, E.; Stone, K.; Tan, L.; Humphrey, G. R.; Chang, D.; Bothe, J.; Zhang, Y.; Bernardoni, F.; Castro, S.; Zompa, M. A.; Taylor, J.; Sirk, K. M.; Diaz-Santana, A.; Diribe, I.; Emerson, K. M.; Krishnamurthi, B.; Zhao, R.; Ward, M.; Xiao, C.; Ouyand, H.; Zhan, J.; Morris, W. J. Development of a Robust Manufacturing Route for Molnupiravir, an Antiviral for the Treatment of COVID-19. *Org. Process Res. Dev.* 2021, 25, 2806–2815. doi.org/10.1021/acs.oprd.1c00400.

- Fischer, W.A.; Eron, J.J.; Holman, W.; Cohen, M.S.; Fang, L.; Szewczyk, L. J.; Sheahan, T.P.; Baric, R.; Mollan, K.R.; Wolfe, C.R. A Phase 2a Clinical Trial of Molnupiravir in Patients with COVID-19 Shows Accelerated SARS-CoV-2 RNA Clearance and Elimination of Infectious Virus. *Sci. Transl. Med.* **2022**, *14*, eabl7430. DOI: 10.1126/scitranslmed.abl7430.
- Gil, C.; Ginex, T.; Maestro, I.; Nozal, V.; Barrado-Gil, L.; Cuesta-Geijo, M. A.; COVID-19: drug targets and potential treatments. *J. Med. Chem.* **2020**, *63*, 12359–12386. DOI: 10.1021/acs.jmedchem.0c00606.
- Gopalsamuthiram, V.; Williams, C.; Noble, J.; Jamison, T. F.; Gupton, B. F.; Snead, D. R.; A Concise Route to MK-4482 (EIDD-2801) from Cytidine: Part 2. *Synlett* **2020**, *32*, 326–328. DOI:10.1055/a-1275-2848
- Gordon, C.J.; Tchesnokov, E.P.; Schinazi, R.F.; Gotte, M. Molnupiravir promotes  $\epsilon$  SARS-CoV-2 mutagenesis via the RNA template. *J Biol Chem* **2021**, *297*, 100770. DOI: 10.1016/j.jbc.2021.100770.
- Hacker, M.; Messer, W.S.; Bachmann, K.A. "Chapter 10.5: Elimination (Metabolism and Excretion)". *Pharmacology: Principles and Practice*. Academic Press. **2009**, 216–217. ISBN: 0080919227, 9780080919225
- Halford, B. "An emerging antiviral takes aim at COVID-19". *C&EN*. Archived from the original on 2 August 2020.
- Hu, B.; Guo, H.; Zhou, P.; Shi, Z.L. Characteristics of SARS-CoV-2 and COVID-19. *Nat. Rev. Microbiol.* **2021**, *19*, 141–154. doi: 10.1038/s41579-020-00459-7.
- Hu, T.; Xie, Y.; Liu, Y.; Xue, H.; Zhu, F.; Aisa, H. A.; Shen, J. "One-Pot" Synthesis of Molnupiravir from Cytidine. *Org. Process Res. Dev.* **2022**, *26*, 2, 358–364. DOI: 10.1055/s-0041-1738031.
- Jornada, D.H.; Dos Santos Fernandes, G.F.; Chiba, D.E.; De Melo, T.R.F.; Dos Santos, J.L.; Chung, M.C. The Prodrug Approach: A Successful Tool for Improving Drug Solubility. *Molecules* **2016**, *21*, 42. DOI: 10.3390/molecules21010042.
- Kabinger, F.; Stiller, C.; Schmitzova, J. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol* **2021** *28*, 740e6. DOI: 10.1038/s41594-021-00651-0.
- Kalal, C.; & Charola, S. An alarming public health concern over variability in herbal compositions of marketed immunity booster products during COVID-19: A botanical survey-based study. *Int. J. Exp. Res. Rev.* **2021**, *24*, 40-50. <https://doi.org/10.52756/ijerr.2021.v24.005>
- Khan, Z.; Karataş, Y.; Rahman, H. Anti COVID-19 drugs: need for more clinical evidence and global action. *Adv. Ther.* **2020**, *37*(6), 2575–2579. DOI: 10.1007/s13337-021-00684-5.
- Liu, Z.; Yang, J.; Liu, F. New Routes to Antiviral Molnupiravir against SARS-CoV-2 Infection. *Chin. J. Org. Chem.* **2022**, *42*, 2988-2993. DOI:10.6023/cjoc202203044
- Markovic, M.; Ben-Shabat, S.; Dahan, A. Prodrugs for Improved Drug Delivery: Lessons Learned from Recently Developed and Marketed Products. *Pharmaceutics* **2020**, *12*, 1031. doi.org/10.3390/pharmaceutics12111031.
- Maurya, R.; Mishra, P.; Swaminathan, A.; Ravi, V.; Saifi, S.; Kankan, A.; Mehta, P.; Devi, P.; Praveen, S.; Budhiraja, S.; SARS-CoV-2 Mutations and COVID-19 Clinical Outcome: Mutation Global Frequency Dynamics and Structural Modulation Hold the Key. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 868414. doi: 10.3389/fcimb.2022.868414.
- McIntosh, J. A., Benkovics, T., Silverman, S. M., Huffman, M. A., Kong, J., Maligres, P. E., Itoh, T., Yang, H., Verma, D., Pan, W., Ho, H., Vroom, J., Knight, A. M., Hurtak, J. A., Klapars, A.,



- Fryszkowska, A., Morris, W., Strotman, N. A., Murphy, G. S., Maloney, K. M., and Fier, P. S., Engineered Ribosyl-1-Kinase Enables Concise Synthesis of Molnupiravir, an Antiviral for COVID-19, *ACS Cent. Sci.* **2021**, *7*, 12, 1980–1985, doi.org/10.1021/acscentsci.1c00608.
- Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke. *Int. J. Stroke* **2018**, *13*, 612–632. DOI: 10.1016/j.jvir.2017.11.026
- Painter, G. R.; Bluemling, G. R.; Natchus, M. G.; Guthrie, D. WO pat., WO2019113462, 2019.
- Painter, G.R.; Bowen, R.A.; Bluemling, G.R.; DeBergh, J.; Edpuganti, V.; Gruddanti, P.R.; Guthrie, D.B.; Hager, M.; Kuiper, D.L.; Lockwood, M.A. The Prophylactic and Therapeutic Activity of a Broadly Active Ribonucleoside Analog in a Murine Model of Intranasal Venezuelan Equine Encephalitis Virus Infection. *Antivir. Res.* **2019**, *171*, 104597. DOI: 10.1016/j.antiviral.2019.104597.
- Painter, W.P.; Holman, W.; Bush, J.A.; Almazedi, F.; Malik, H.; Eraut, N.C.J.E.; Morin, M.J.; Szewczyk, L.J.; Painter, G.R. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. *Antimicrob. Agents Chemother* **2021**, *65*, e02428-20.
- Pereira, V. R. D.; Bezerra, M. A. M.; Gomez, M. R. B. P.; Martins, G. M.; da Silva, A. D.; de Oliveira, K. T.; de Souza, R. O. M. A.; Amarante, G. W. Concise two-step chemical synthesis of molnupiravir. *RSC Adv.* **2022**, *12*, 30120-30124. doi.org/10.1039/D2RA05064A.
- Rautio, J.; Meanwell, N.A.; Di, L.; Hageman, M.J. "The expanding role of prodrugs in contemporary drug design and development". *Nature Reviews. Drug Discovery.* **2018**, *17* (8): 559–587. doi.org/10.1038/nrd.2018.46.
- Rosangzuala, K., Patlolla, R. R., Shaikh, A., Naik, K. A. P., Raveena, G., Nemali, M., Mudiam M. K. R.\*, and Banoth, L., \* Streamlined Chemo-Enzymatic Synthesis of Molnupiravir via Lipase Catalyst, *ACS Omega* **2024**, *9*, 4, 4423–4428, doi.org/10.1021/acsomega.3c06872.
- Roychoudhury, S.; Das, A.; Jha, N.K.; Kesari, K.K.; Roychoudhury, S.; Jha, S.K.; Kosgi, R.; Choudhury, A.P.; Lukac, N.; Madhu, N.R.; Kumar, D.; & Slama, P. Viral pathogenesis of SARS-CoV-2 infection and male reproductive health. *Open Biology* (The Royal Society Publishing, UK), **2021**, *11*, 200347 (Page 1- 11). https://doi.org/10.1098/rsob.200347.
- Sahoo, T.; Reddy, B.V.S. Concise synthesis of antiviral drug, molnupiravir by direct coupling of fully protected D-ribose with cytosine. *Tetrahedron Lett.* **2022**, *97*, 153783. doi.org/10.1016/j.tetlet.2022.153783.
- Sezer, A.; HalilovićAlihodžić, M.; Vanwieren, A.R.; Smajkan, A.; Karić, A.; Djedović, H.; Šutković, J. A review on drug repurposing in COVID-19: from antiviral drugs to herbal alternatives. *J. Genet. Eng. Biotechnol.* **2022**, *20*, 78. DOI: 10.1186/s43141-022-00353-0.
- Sharma, A.; Ahmed, S.; Kaur, J.; Chawla, R.; Rejeeth, C. Exploring status of emergency drugs and vaccine development in Covid-19 pandemic: an update. *VirusDisease* **2021**, *32*, 198–210.
- Steiner, A.; Znidar, D.; Otvös, S. B.; Snead, D. R.; Dallinger, D.; Kappe, C. O. A High-Yielding Synthesis of EIDD-2801 from Uridine. *Eur. J. Org. Chem.* **2020**, 6736–6739. DOI:10.26434/chemrxiv.13058486.v1.
- Teli, D.; Balar, P.; Patel, K.; Sharma, A.; Chavda, V.; Vora, L. Molnupiravir: A Versatile Prodrug against SARS-CoV-2 Variants. *Metabolites.* **2023**, *13*, 309. DOI: 10.3390/metabo13020309.
- Toots, M.; Yoon, J.J.; Cox, R.M.; Hart, M.; Sticher, Z.M.; Makhous, N.; Plesker, R.; Barrena, A.H.; Reddy, P.G.; Mitchell, D.G.; Characterization of orally efficacious influenza drug with high

resistance barrier in ferrets and human airway epithelia. *Sci. Transl. Med.* **2019**, *11*, eaax5866. DOI: 10.1126/scitranslmed.aax5866

Toots, M.; Yoon, J.J.; Hart, M.; Natchus, M.G.; Painter, G.R.; Plemper, R.K. Quantitative Efficacy Paradigms of the Influenza Clinical Drug Candidate EIDD-2801 in the Ferret Model. *Transl. Res.* **2020**, *218*, 16–28. DOI: 10.1016/j.trsl.2019.12.002.

Vashist, P.; Vashist, R.; & Tripathi, A. Scientific Assessment and Sorting of Topological Parameters Affecting Time in Recovering from COVID-19. *Int. J. Exp. Res. Rev.*, **2023**, *30*, 359-365. <https://doi.org/10.52756/ijerr.2023.v30.033>

Vasudevan, N.; Ahlqvist, G. P.; McGeough, C. P.; Paymode, D. J.; Cardoso, F. S. P.; Lucas, T.; Dietz, J. P.; Opatz, T.; Jamison, T. F.; Gupton, F. B.; Snead, D. R. A concise route to MK-4482 (EIDD2801) from cytidine. *Chem. Commun.* **2020**, *56*, 13363–13364. [doi.org/10.1039/D0CC05944G](https://doi.org/10.1039/D0CC05944G).

Venkatanarayana, P.; Kolli, D.; Seelama, N. V.; Ramakrishna, D. S. Synthesis of molnupiravir (MK-4482, EIDD-2801): a promising oral drug for the treatment of COVID-19 starting from cytidine. *Nucleosides, Nucleotides & Nucleic Acids*, **2023**, *42*, 427–435. DOI: 10.1080/15257770.2022.2153140.

Wang, Z.; Yang, L. Broad-Spectrum Prodrugs with Anti-SARS-CoV-2 Activities: Strategies, Benefits, and Challenges. *J. Med. Virol.* **2022**, *94*, 1373–1390. DOI: 10.1002/jmv.27517.

Yip, A.J.W.; Low, Z.Y.; Chow, V.T.K.; Lal, S.K. Repurposing Molnupiravir for COVID-19: The Mechanisms of Antiviral Activity. *Viruses* **2022**, *14*, 1345. DOI: 10.3390/v14061345.

Yoon, J.J.; Toots, M.; Lee, S.; Lee, M.E.; Ludeke, B.; Luczo, J.M.; Ganti, K.; Cox, R.M.; Sticher, Z.M.; Edpuganti, V.; Orally Efficacious Broad-Spectrum Ribonucleoside Analog Inhibitor of Influenza and Respiratory Syncytial Viruses. *Antimicrob. Agents Chemother.* **2018**, *62*, e00766-18. DOI: 10.1128/AAC.00766-18.

## HOW TO CITE

T. Sahoo, P. Shrivastava, A. Chandra, S. K. Biswas and B. V. Subba Reddy (2024). The Biological Activity and Synthesis of Orally Active COVID-19 (SARS-CoV-2) Antiviral Drug Molnupiravir. © International Academic Publishing House (IAPH), Dr. Suman Adhikari, Dr. Manik Bhattacharya and Dr. Ankan Sinha, *A Basic Handbook of Science, Technology and Innovation for Inclusive Development [Volume: 1]*, pp. 13-39. ISBN: 978-81-969828-4-3 DOI: <https://doi.org/10.52756/bhstiid.2024.e01.002>

