Research Article

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MOLNUPIRAVIR: A Promising Antiviral for COVID-19

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Abstract

Covid 19 is a pandemic which has affected the whole world. As time passed by mid of February 2020 it was declared as a global pandemic by the WHO. Many people lost their lives due to improper treatment and insufficient knowledge and unavailable hospital treatment about this novel virus. In this article the origin of coronavirus, methods and medicines used in the past to contain it are mentioned. Further this article discusses the newly discovered novel drug molnupiravir, its structure, synthesis, mechanism of action and its effectiveness in treatment of Covid 19. It also mentions the difference between remdesivir and molnupiravir. In synthesis, previous and present approaches are discussed

Keywords- Molnupiravir, Covid 19, Synthesis, Remdesivir

1. INTRODUCTION

In December 2019, in the Wuhan Hubei province of China, an unknown outburst of respiratory difficulties leading to severe pneumonia with an unknown origin was reported. [1,2] Soon months passed and by the mid of 2020, this unknown entity captured the entire world.[3] Further when the samples from epithelial cells of the respiratory tract were isolated to check for the causative agent. It led to the discovery of a novel strain coronavirus which was happened to be associated with SARS-CoV hence the name 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV2). [4] As this virus was spread worldwide and caused thousands of deaths before February 2020, The World Health Organisation (WHO) declared Covid-19 to be a global pandemic.[5] After the discovery of this virus, it was still difficult to contain this virus without a proper line of treatment or even without a proper cure. The only way out of this was to develop a viable vaccine or to discover a reliable line of treatment to eradicate this virus. Until then only measures that people could rely on were wearing a mask, constantly sanitizing hands, and social distancing. Treatment that doctors followed back then just included building immunity of the patient so that his/her immune system can self-repair. Scientists also tried using anti-malarial agents like hydroxychloroquine which in turn helped a bit in improving the symptoms for a while.[6] Further, the use of antivirals was also found to be useful in alleviating the severity of the situation. The perfect candidate at that time seemed to be remdesivir and favipiravir, to check its effectiveness intravenous randomized, placebo-controlled trials, were carried out on the patient suffering from severe Covid-19 infection.[7–9] The primary outcome was they observed a reduction in the severity of the situation, reduced respiratory infection and soon the patients were discharged over a period of a certain amount of time. During the second wave of COVID-19, in India sales of Remdesivir were touching skies, as a result, its prices were higher than ever and its availability was still questionable.[10] Before even the last phase trials ended many scientists and doctors started questioning its effectiveness. Further, it was found out that it is not

recommended for patients suffering from renal dysfunction.[11] It was found out when patients were given remdesivir and observed. The patients with creatine clearance of <30ml/min showed good results but whereas in patients with creatine clearance >30ml/min majority of the patients were on vasopressors the day remdesivir therapy started and it was further followed by mechanical ventilation as the therapy progressed.[12,13] Not only in case of renal insufficiency but remdesivir also proved to be a matter of concern in patients with diabetes as their sugar levels fluctuated on remdesivir administration.[14,15] Remdesivir helped a bit in improving the symptoms but because of its side effects profile, high prices, unavailability and various routes of administration which could only be fulfilled in a medical facility and cannot be taken in patients with home isolation. Now it became important for doctors and scientists to come up with a better solution till the major population will be vaccinated. Molnupiravir was developed initially to treat influenza, but it has been repurposed to treat COVID 19 infection as it interferes in the replication of SARS-CoV-2, consequently reducing the severity of the disease.[16,17] Therefore, Researchers in recent trials saw a potential drug for effective treatment of COVID 19, the first oral antiviral drug molnupiravir as other currently authorized drugs are administered intravenously or injected. Trials showed that it halved the risk of hospital admissions and deaths from COVID-19. Scientists claim that molnupiravir can become an important medicine to fight the pandemic. Molnupiravir was found to be very efficacious in a phase 3 trial involving COVID-19-positive people at risk of severe illness.[18–2]

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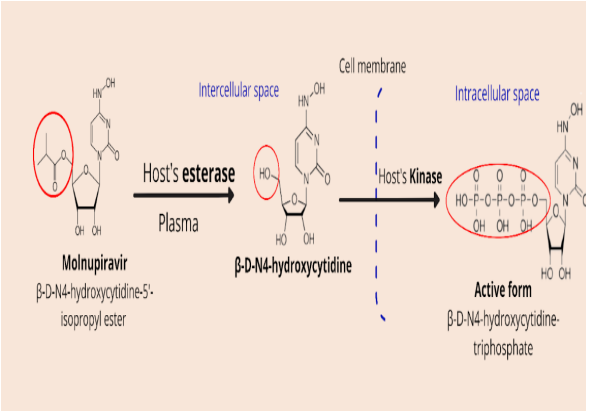
2. STRUCTURE OF MOLNUPIRAVIR

Molnupiravir, known as β-d-N4-hydroxycytidine-5′-isopropyl ester and it is a prodrug of β-d-N4-hydroxycytidine. It is rapidly converted into β-d-N4-hydroxycytidine in the plasma by the host's esterase.[21] It enters the host cells, and it is bio-transformed into its active form, β-d-N4-hydroxycytidine-triphosphate intracellularly.[21] The antiviral action is elucidated by inducing copying errors during the replication of RNA. [22]

Formula $C_{13}H_{19}N_3O_7$

Formula 329.309 $g \cdot mol^{-1}$



Ref: https://doi.org/10.3390/antibiotics10111294

3. SYNTHESIS

3.1 PREVIOUS APPROACHES

Previous approaches for the synthesis of molnupiravir are as follows:

1. Uridine was used to synthesize molnupiravir. It consisted of 4 to 5 steps and the overall yield obtained was 17%. This route was initially used by Emory university.[23]

2. Kappe and co-workers improved the process of synthesis of molnupiravir from uridine by carrying out it in four steps. But the disadvantage in this route was the reagent 1,2,4-triazole was very expensive. [23]

3. Cytidine was also used to synthesize molnupiravir. The reaction was completed in two steps by Novozyme-435-catalyzed esterification of C5-OH using isobutyryl acetone oxime ester. But the enzyme used Novozyme-435 lead to many problems such as enzyme leaching leading to contamination, high cost, catalyst recycling, etc. [24–27]

4. D-ribose was used as starting reagent to synthesize molunpiravir as it was cheaper and completed the reaction in three steps. This method was given by Fier and co-workers. However, this method also involved Novozyme-435 for esterification, and the solvent used HMDS (Hexamethyldisilazane) was costly.[28]

Hence more competent and economical methods with inexpensive chemicals were discovered.

3.2 PRESENT APPROACH

a. In this approach, uridine is used as a starting material, which undergoes acetonation in presence of H_2SO_4 at position C2' and C3' hydroxyl groups

respectively. This reaction occurs at room temperature.[29]

b. After acetonation, esterification at position C5' takes place under favourable conditions using isobutyric anhydride, DMAP (4-dimethylaminopyridine), MeCN (acetonitrile), Et3N (Triethylamine) in room temperature.[29]
c. The unrefined product obtained after esterification, is then reacted with lawesson's reagent and toluene to give the pure intermediate product under optimum condition. The intermediate product gave 81% yield after chromatographic separation.[29]
d. The intermediate product obtained, was then reacted with aqueous hydroxylamine in presence of MeOH for a time of 1 hour to give oxime. immediately, after the reaction, the menthol was discarded under reduced pressure. In the residue left, formic acid was added at room temperature to obtain pure molnupiravir. This reaction yielded 62% of pure molnupiravir having more than 99% purity seen after chromatographic separation.[29]

4. MECHANISM OF ACTION

Now let us go in-depth and discuss its mechanism of action. Molnupiravir is not the main drug that acts upon the body but whereas it's an isopropyl ester prodrug of N-4-Hydroxycytidine. As it has enhanced oral bioavailability it is hydrolysed in vivo in the case of nonhuman primates where is acts onto the tissues and gets converted to its active 5'-triphosphate form.[21] Further, this active substance interferes with the genome or RNA viruses which results in mutational accumulation leading to viral error catastrophe.[20,22] As discussed in the introduction use of molnupiravir seems to be of use in inhibiting coronavirus replication in the case of humans. Let us try to go in-depth and understand the mechanism. So when it comes to coronavirus it replicates and transcripts using an RNA-dependent RNA polymerase(RdRp).[30] So inhibition of this RdRp is of importance while discovering antivirals against Covid 19. Generally, antivirals act by targeting viral polymerase and function and hence the RNA chain elongation is terminated.[31] But in the case of Coronavirus, it has an exonucleolytic proofreading activity with enables it to remove disincorporated nucleotides.[30,32] So after further research it was found out that molnupiravir can be a valuable candidate as it can target RdRp and hence can inhibit coronavirus replication. So molnupiravir acts by inhibiting Covid 19 replication in lungs tissues and further it terminates SARS-CoV-2 transmission in ferrets.[33] This leads to decreased transmission amongst patients. Further Molnupiravir can enhance G to A and C to U transformation mutation in replicating Covid 19 virus.[30,32] These increased mutations can be considered to be in association with its increased antiviral activity

5. CONCLUSION

Molnupiravir drug was initially developed to treat influenza, but scientists manifested that it could be an effective drug to combat Covid-19 infection. Molnupiravir is the first oral, direct-acting antiviral highly effective at reducing SARS-CoV-2 infection and has a favourable safety and toxicity profile. Molnupiravir ceases the viral replication by the "error catastrophe" mechanism. Molnupiravir acts on the RdRp enzyme and competing with uridine and cytidine triphosphate substrates leads to the incorporation of A and G forming stable complexes in the active RdRp centre inducing mutagenesis and escaping proofreading. the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for Merck's molnupiravir for the treatment of mild-to-moderate coronavirus disease (Covid-19) in adults with positive results of direct SARS-CoV-2 viral testing, and who are susceptible for moderate to severe Covid-19, including hospitalization or death, and for whom other Covid-19 treatment options authorized by the FDA are not accessible or clinically appropriate.[34]

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Conflict of Interest

The authors have no conflict of interest.

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