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Review Article……!!!

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A REVIEW OF – FAVIPIRAVIR MECHANISM ACTION OF COVID-19

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Keywords:

Favipiravir, SARS-CoV-2 RNA polymerase, radiological improvement

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ABSTRACT

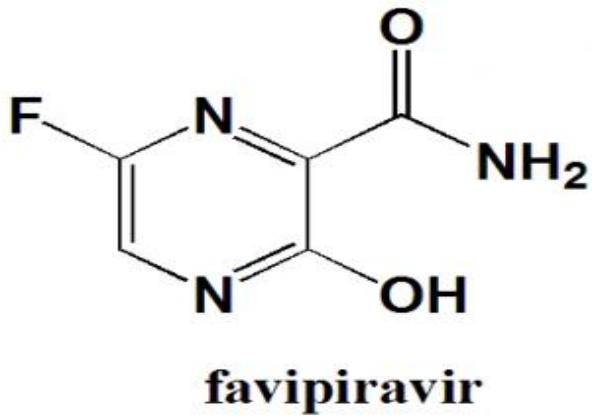
Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an anti-viral agent that selectively and potently inhibits the RNA-dependent RNA polymerase of RNA viruses. Favipiravir is backed by strong clinical evidence showing encouraging results in patients with mild to moderate COVID-19. The antiviral offers broad spectrum RNA virus coverage with clinical improvement noted across age groups 20 to >90 years. Favipiravir can be used in COVID-19 patients with co-morbid conditions such as diabetes and heart disease with mild to moderate COVID 19 symptoms. It offers rapid reduction in viral load within 4 days and provides faster symptomatic and radiological improvement. Favipiravir has shown clinical improvement of up to 88% in COVID-19 mild to moderate COVID 19 cases. Favipiravir is approved in Japan since 2014 for the treatment of novel or re-emerging influenza virus infections. It has a unique mechanism of action: it is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and recognized as a substrate by viral RNA polymerase, thereby inhibiting RNA polymerase activity. The emergence of COVID-19 as a pandemic has resulted in the need for urgent development of vaccines and drugs and the conduction of clinical trials to fight the outbreak. Because of the time constraints associated with the development of vaccines and effective drugs, drug repurposing and other alternative treatment methods have been used to treat patients that have been infected by the SARS-CoV-2 virus and have acquired COVID-19.

INTRODUCTION

In December 2019, a novel type of viral pneumonia was discovered in Wuhan, Hubei Province, China. The International Committee of Taxonomy of Viruses has officially named the disease "COVID-19 (Corona Virus Disease 2019)" and the virus SARS-CoV-2 [1,2]. The new corona virus has rapidly spread among humans all over the world and has led to hundreds of thousands of cases within a few months. As a result, on 11th March 2020 the World Health Organization (WHO) declared COVID-19 a pandemic, which is defined as "worldwide spread of a new disease. The initial stage occurs at the time of inoculation and early establishment of the disease. For most people, this involves an incubation period associated with mild and often non-specific symptoms such as malaise, fever, and a dry cough. During this period, SARS-CoV-2 multiplies and establishes residence in the host, primarily focusing on the respiratory system. SARS-CoV-2 binds to its target using the angiotensin-converting enzyme (ACE2) receptor on human cells. Favipiravir was discovered by chemical modification of a pyrazine analog initially screened By in vitro anti-influenza virus activity in cells. Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase, and effective against all subtypes and strains of influenza viruses including ones sensitive or resistant to marketed neuraminidase and M2 inhibitors. Favipiravir demonstrated anti-viral activities against other RNA viruses.

IUPAC Nomenclature:

6-Fluoro- 3-hydoxypyrazine-2 carboxamide.



favipiravir

Physiochemical Properties:

S. NO.	Physical and Chemical Properties	
1	Molecular weight	157.1 g/mol
2	Physical appearance	Light yellow to yellow solid
3	Melting point	187-193°C
4	Solubility	Slightly soluble in water
5	Presence of ring	Pyrazine
6	Number of chiral centers	Not present

MECHANISM OF ACTION

Favipiravir interacts with RNA dependent RNA polymerase. It prevents the elongation of the RNA strand and viral proliferation by incorporating into nascent RNA strand. Thus, it selectively inhibits RNA polymerase and prevents replication of the viral genome.

SAR:

- Modified 2'C-methyl-NTP analogs causes immediate chain termination.
- Smaller compounds with pyrazine ring are docked deeper but relatively smaller pocket of VP35.
- For proper binding with VP35 IID, essential benzene rings and pyrrilidinone scaffold are required. [1]

MATERIALS AND METHOD

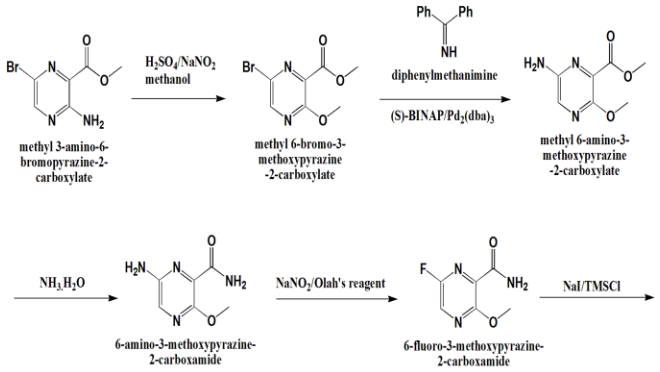
i. Methyl 3-amino-6-bromopyrazine-2-carboxylate undergoes reaction with sodium nitrite in presence of acid to produce methyl 6-bromo-3-methoxypyrazine-2-carboxylate.

ii. The above compound undergoes reaction with diphenylmethanamine to methyl 6-amino-3-methoxypyrazine-2-carboxylate.

iii. It then undergoes reaction with ammonia water to produce 6-amino-3-methoxypyrazine-2-carboxamide.

iv. Compound is thereafter reacted with sodium nitrite in presence of Olah's reagent to produce 6-fluoro-3-methoxypyrazine-2-carboxamide.

v. The above formed compound is then reacted with sodium iodide in TMSCl to yield favipiravir.



USES OF FAVIPIRAVIR

- Treatment of Influenza A and B viruses
- Treatment of Ebola virus (on trial)
- Treatment of Yellow fever (on trial)
- Treatment of Nipah virus (on trial)

DISCUSSION

As of recent, favipiravir was one of the experimental drugs on trial for COVID-19, a viral infection caused by the novel coronavirus, SARS-CoV-2. so far the drug has shown an 80% efficacy and its moving to the third phase of the trial against COVID-19. The underlying mechanism of the favipiravir is the metabolization of its active form which inhibits the action of RNA-dependent RNA polymerase stopping transcription and replication. The initial study was done in Japan and China in February 2020 with evidence of the reduced time of viral clearance.

(https://www.pharmaceutical-technology.com/news/fujifilm-favipiravir-covid-19/)

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