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Review Article

A REVIEW ON THE DEVELOPMENT OF FAVIPRAVIR AGAINST SARS COV 2 INFECTION

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ABSTRACT

Covid 19, the disease first identified in the Chine city of Wuhan in December 2019 had been declared as a pandemic by WHO. This pandemic caused by Sars Cov 2 has resulted in 165.5 million infections and 3.5 million deaths globally, as of now. Till now no drug isavailable to fight against this deadly disease. The strategy adopted by drug discovery groups is drug repurposing which has not met much success with chloroquine as well as remdesivir. A relatively new candidate in the fray is favipravir which was originally developed by Toyama chemical company against influenza strains. Few synthetic routes are developed for this compound and the safety concerns are relatively few. If favourable results from the ongoing clinicaltrials arise, that may provide the therapeutic community a lethalweapon against the virus.

Keywords: Favipravir, Sars Cov 2, Drug Repurposing, Purine nucleoside, Chemical synthesis, Clinical trials, FPV

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INTRODUCTION

Sars Cov 2, which was first identified in the Chinese city of Wuhan has been declared as a pandemic by the WHO in Feb 2020 [1]. The exact cause of the outbreak of this pandemic is yet to be identified by scientists. The viral reservoir is beleived to be the native bat population and it is hypothesed that the first transmission would have occured from a wild meat market in Hubei province in China [2]. The disease then spread to different countries and had accounted for 165.5 million infections and 3.5 million deaths globally. The pandemic has become a public health and economic burden worldwide. The morphology of Sars Cov 2, molecular mechanisms behind the viral entry, infective process and replication have now been well known to the research community [3-11].

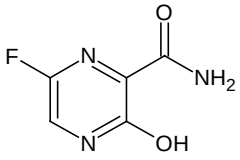
The capability to mutate rapidly and to aquire genetic changes frequently by the virus is acting as great obstacles for drug discovery scientists to introduce a novel therapeutic agent to fight against covid-19 [12].

The tool widely used to fight against this pandemic is the drug repurposing strategy which has a coming of age effect in the present scenario. Few antivirals like remdesivir, favipravir etc has been introduced into clinical practice against sars cov 2 and their effectiveness is still under debate. In the present article a detailed review is attempted about the development and efficacy of favipravir, as an anti covid medication.

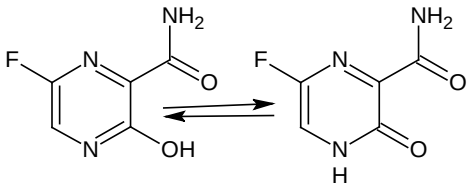
Favipravir was invented by Toyama chemical co. Japan in 2002 and was introduced as a therapy for infections by influenza virus. It could be effectively used against infleunza A, B and C infections. It is a broad-spectrum antiviral agent and is known to be active against bunyavirus, yellow virus, West Nile fever virus as well as influenza and ebola. It also has inhibitory effects on human norovirus and human arenavirus [13, 14].

Chemistry of favipravir

Favipravir chemically is a pyrazine carboxamide and it can be regarded as a purine nucleoside analogue.



The chemical name of FPV is 6-fluoro-3-oxo-1*H*-pyrazine-2-carboxamide. Its molecular formula is C5H4FN3O2 and the molecular weight is 157. 02. FPV is slightly soluble in water and is soluble in organic solvents. Due to the presence of the hydroxy group, the compound is acidic and is expected to exhibit keto-enol tautomerism [15].



Enol Form Keto form

Polymorphism of favipravir

Favipravir reportedly exhibits polymorphism. FPV predominantly exists as orthothrombic polymorph. Goloveshkin *et al.* had identified a tetragonal polymorph with crystal parameters similiar to those of the known orthothrombic polymorph. The orthothrombic polymorph is readily formed from solvents and posess a more wide spreadigng H-bond architecture. The two tetragonal form gets converted to orthothrombic form at room temperature [16].

Chemical synthesis of favipravir

Many synthetic routes for FPV has been formulated by various research groups with the original route employing 2-amino–bromo pyrazine-1-carboxylate as the starting material. This route includes five steps and the steps are diazotization/alcoholysis, imine substitution/hydrolysis catalyzed by Pd, aminolysis, Schiemann fluorination and demethylation [17]. This scheme is presented in fig. I.

Scheme of synthesis of favipravir

Several synthetic schemes of FPV were introduced by drug syntheitic groups and most of these schemes employ 3-amino pyrazine 2-carboxylic acid as the starting material with modifications in the succeeding steps [18]. This synthesis is presented in scheme 1. A completely different scheme of synthesis is reported by Titova *et al.* where diethyl malonate is the starting material and the synthesis includes isoxazole ring formation and cleavage in subsequent steps [19]. This scheme is presented in fig. 2.

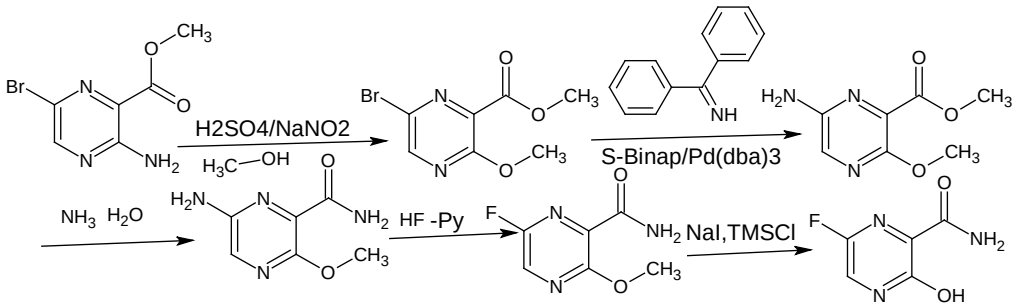


Fig. 1: Scheme I

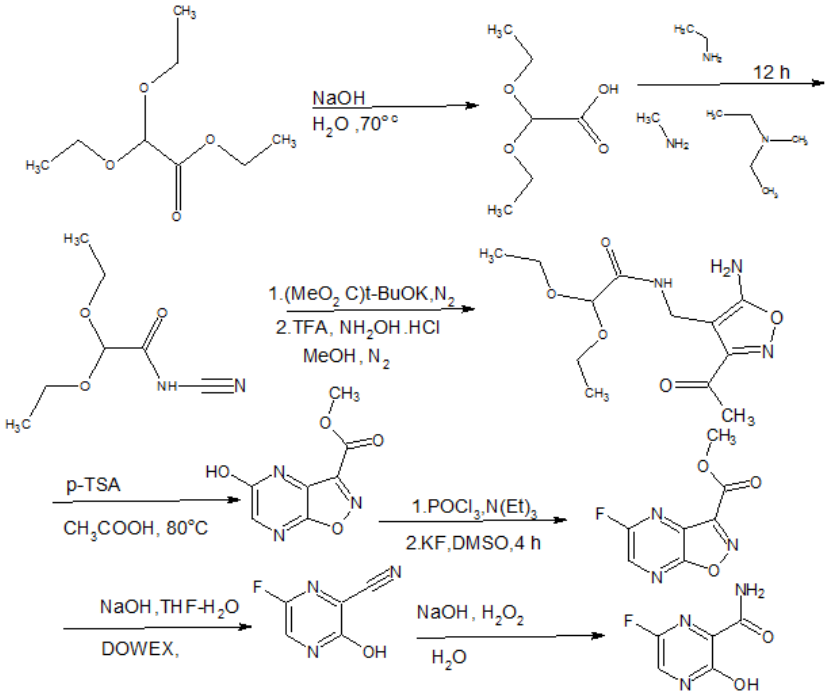


Fig. 2: Scheme II

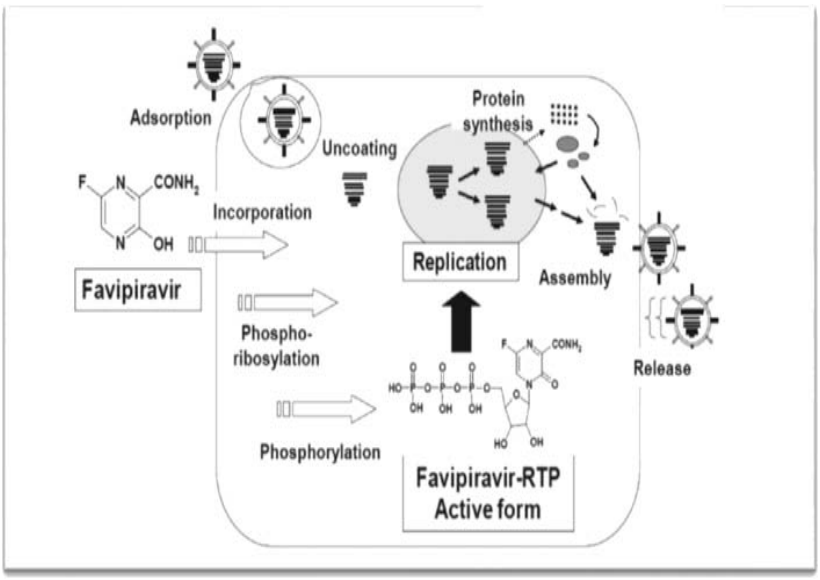


Fig. 3: Mechanism of action of FPV

Mechanism of action of favipravir

FPV is a prodrug that becomes activated by ribosylation and phosphorylation. The active cellular form is FPV-ribosyl-5-triphosphate. FPV binds and inhibits RdRp, which is ultimately preventing viral genome RNA transcription and replication. The ribosylated and triphosphorylated active metabolite TP705 inhibits RdRp by chain termination of the nascent viral RNA strand. It is also hypothesed to act by binding with conserved viral polymerase domains thus preventing incorporation of nucleotides for viral RNA replication and transcription [20]. Previous studies suggest that favipiravir has virucidal effects, implicating the mutagenesis by favipiravir may be engaged in various types of RNA viruses. Compared to viral cells human cells do not have RdRp, but have DNA-dependent RNA polymerase. (DdRp) and DNA-dependent DNA polymerase.(DdDp) FPV does not have inhibitory effects on these enzymes.[21] The schematic representation of the mechanism of action is presented in fig. 3.

Pharmacokinetics of favipravir

The drug FPV is absorbed from the oral route and is bound to plasma protein by 54% in humans [22]. The drug follows nonlinear kinetics.(Du and Chen 2020) The major portion of FPV administered will be distributed to the liver, kidney, brain tissue and stomach [23].

The drug is metabolized by aldehyde oxygenase (AO) mainly and partially by xanthine oxidase(XO) [24]. FPV is known to inhibit the activity of AO. The product of the metabolism is an inactive oxidative metabolite. Mainly the kidneys excrete the inactive metabolite. Un metabolized FPV and metabolites were identified in semen and breast milk [25].

Adverse effects

In the reported clinical trials, FPV was well tolerated. However, it is related to dose-dependent, asymptomatic increases in serum uric acid levels and must be administered with caution in patients with a history of gout. Caution is advised in patients with hyperuricemia. The adverse effects may also include mild to moderate diarrhoea [26].

Drug-drug interactions

A potential risk of drug interaction occurs between the drugs that inhibit aldehyde oxidase, and favipiravir administration needs to be monitored cautiously. There is a risk of interaction of FPV with pyrazinamide, repaglinide, theophylline, famciclovir, and sulindac [27].

Effectiveness of favipravir in sars Cov-2 infection

In a pre-clinical study conducted by Driouich *et al.* by Syrian hamster model FPV administration has reportedly reduced infectious titers in the lungs and clinical alleviation of the disease [28].

In clinical trials conducted, FPV has been found to be effective in controlling disease progression and in enhancing viral clearance in COVID-19 patients [29]. (Takahashi *et al.* 2020) Apart from being administered alone, FPV can be used along with other drugs or therapies to tackle COVID19. According to Dabbous *et al.* (2021) in a multicenter randomized controlled study, FPV was known to reduce the hospital stay and need for mechanical ventilation in Sars Cov-2 infected patients [30].

CONCLUSION

The pandemic SARS COV-2 has shattered global public health and the economy irrecoverably. Due to the rapidly mutating nature of the virus, the discovery of an effective medication seems to be an uphill task. An attempt to introduce an anti-Sars Cov-2 medication is through drug repurposing. Agents like chloroquine, dexamethasone, ivermectin, remdesivir were few of the repurposed agents, but the results were not very promising. A relatively new entrant in the repurposed category in the fight against Sars Cov-2 is Favipravir, originally developed against influenza strain. Compared to the above-mentioned agents, the early clinical trials of FPV gave promising results. The comparatively simple chemical structure, analogousness to purine nucleosides, is an advantage in the synthetic process and the ADME parameters are non-complicated. If positive results from the ongoing trials are declared soon, with sincere hope, it can be expected that the end of the darkest era in modern human history can be seen.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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