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Review Article

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REVIEW ARTICLE: FAVIPIRAVIR AS AN ANTIVIRAL DRUG

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ABSTRACT

Favipiravir is a RNA polymerase inhibitor, has been proved to have potent inhibitory activity against RNA viruses in vitro & in vivo. In recent times it has shown activity against COVID- 19 also. Synthesis routes to Favipiravir can be divided into two categories, with one category being the reactions developed by the innovator Toyama Chemical Company and the other group being reactions developed by academia and generic companies. Favipiravir's side effects are also discussed in this review. Favipiravir's efficacy gets varied when interacted with other drugs such as pyrazinamide, repaglinide, theophylline, famciclovir, sulindac and acyclovir.

KEYWORDS: Favipiravir, T-705, Influenza, COVID-19, Ebola.

INTRODUCTION

Favipiravir (T-705, 6-fuoro-3-hydroxypyrazine-2-carboxamide) is a novel anti-influenza drug which functions to selectively inhibit the RNA-dependent RNA polymerase of influenza virus.[1] In the active form it is T-705 ribofuranosyl triphosphate, generated from the parent drug by a series of intracellular enzymes.[2, 3] Moreover, favipiravir exhibits inhibitory effects against a variety of other pathogenic RNA viral infections, including those caused by the arena virus, bunya virus, favivirus, alpha virus, and norovirus.[4,5] Favipiravir also can be a promising therapeutic candidate for infection caused by Ebola virus.[6] Patients who received T-705 in a retrospective clinical research conducted during the Ebola virus outbreak had significantly higher viral loads reduction than those in the control group.[7] Recently, Favipiravir and related structures have attracted extensive attentions in the field of antiviral and antiparasitic research.[8-13] It would take a lot of time and effort to find a novel antiviral drug that is specifically effective against the SARS-CoV-2. The COVID-19 epidemic, which started in China's Hubei Province in December 2019, has devastated all continents except for Antarctica. COVID-19 is an infectious disease associated with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a novel coronavirus. Even though the world has previously survived several pandemics, this one is a new global health threat that has fundamentally changed how we live and is still having a terrible socioeconomic impact on people all across the world. Hence, by default, medications that were already being used to treat other viral illnesses have been put into action. Favipiravir is one such medication. It was first sold in Japan as an anti-influenza drug. The Drug Controller General of India has given this drug emergency permission (DCGI). The first time favipiravir was used to treat SARS-CoV-2 was in Wuhan, the pandemic's actual epicenter. Once the virus spread to Europe, the drug was authorized for use in an emergency in Italy. It is also used in Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan. Saudi Arabia and the United Arab Emirates have also given their approval. Bangladesh, Turkey, and so on will follow. Favipiravir acquired the DCGI approval for mild and moderate COVID-19 infections in India in June 2020. There are 32 studies registered on clinical trials.gov as of July 23, 2020, to evaluate the effectiveness of this medication in the treatment of COVID-19.[14]

Favipiravir sold under the trade name Avigan is a novel broad-spectrum, low molecular weight antiviral developed by Toyama Chemical Company [Figure1]. This modified pyrazine analogue was approved in Japan as an anti-influenza medicine, and is known to inhibit replication of influenza A and B. Favipiravir has shown activity against avian influenza and for many other RNA type viruses.[15] The apparent lack of development of favipiravir- resistant viruses is Favipiravir's finest antiviral property. From the first to the last patient in an influenza pandemic or epidemic deadly RNA virus infection, this medication maintains its therapeutic efficacy when used as solo treatments. In an experimental model of a deadly influenza infection, favipiravir was found to cure every mouse. Favipiravir thus aids in the recovery of animals who have a fatal infection. Although it is still difficult to anticipate when

an avian influenza pandemic would begin, one technique used to combat pandemics is to stockpile vaccinations and anti-influenza medications for new strains of the virus. Favipiravir is thought to play a key role among anti-influenza medications in the management of a claimed deadly influenza pandemic due to its unique properties, method of action, and lack of ability to breed virus resistance.

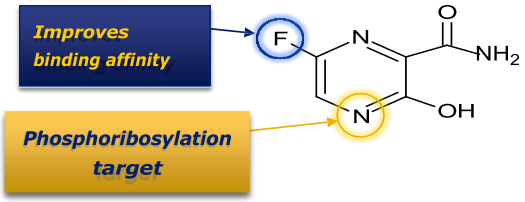


Figure 1– Favipiravir structure.

Sr. No.	PROPERTIES	
1	Molecular Weight	157.1 gm/mol
2	Physical Appearance	Light 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

DISCUSSION

TAUTOMERISM

Favipiravir can exist in several different tautomeric forms. Mirzaei and coworkers reported the structural analysis of Favipiravir and examined the tautomeric structures of Favipiravir [Figure 2] using DFT calculations. Further studies involved calculation of molecular properties and subsequent docking studies on COVID-19 related enzymes. Structural analysis revealed tautomer T3 (-380891 kcal/mol) to be energetically favorable over tautomer T1 (-380886 kcal/mol) by 5 kcal/mol. The other two tautomers were less stable with energy values of - 380871 kcal/mol for tautomer T2 and - 380876 kcal/mol for tautomer T4. Although T3 was the most stable tautomer, tautomer T1 was the most active against protease and polymerase macromolecules. In spite of lower energy, synthesis routes reported tautomer T1 instead of tautomer T3 as the final isolated product.[16]

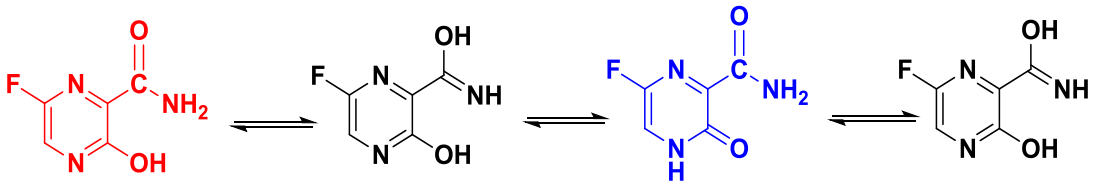


Figure 2– Tautomerism in Favipiravir structure.

This compound is a pro-drug, it is phosphoribosylated in cells to Favipiravir triphosphate, which inhibits viral replication. The fluoro group in the structure improves Favipiravir binding energy with the RNA polymerase. The literature shows that the nitrogen atom that suffers phosphoribosylation is a good target for structural modifications, although the attempts to obtain the Favipiravir riboside or the monophosphate showed that its bond is prone to cleavage and the compound had poor solubility.

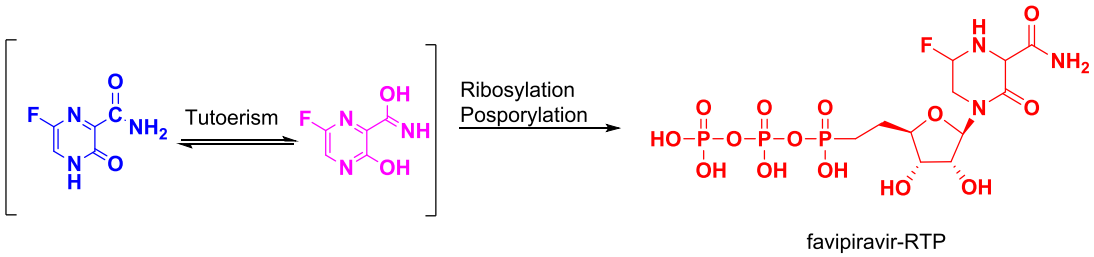


Figure 3: Favipiravir-RTP.

MECHANISM OF ACTION

Within the tissue, the molecule undergoes phosphoribosylation to favipiravir-RTP, which is the active form of this drug. It exerts its antiviral effect through the following mechanisms.

A. This molecule acts as a substrate for the RNA-dependent RNA-polymerase (RdRp) enzyme, which is mistaken by the enzyme as a purine nucleotide, thus inhibiting its activity leading to termination of viral protein synthesis [Figure 4].

B. It gets incorporated in the viral RNA strand, preventing further extension. This mechanism of action, along with preservation of the catalytic domain of the RdRp enzyme across various RNA viruses, explains the

broad spectrum of activity of this drug.[26]

C. It has recently been shown that favipiravir induces lethal mutagenesis in vitro during influenza virus infection, making it a virucidal drug. Whether a similar activity is demonstrated against SARS-CoV-2 or not is uncertain.

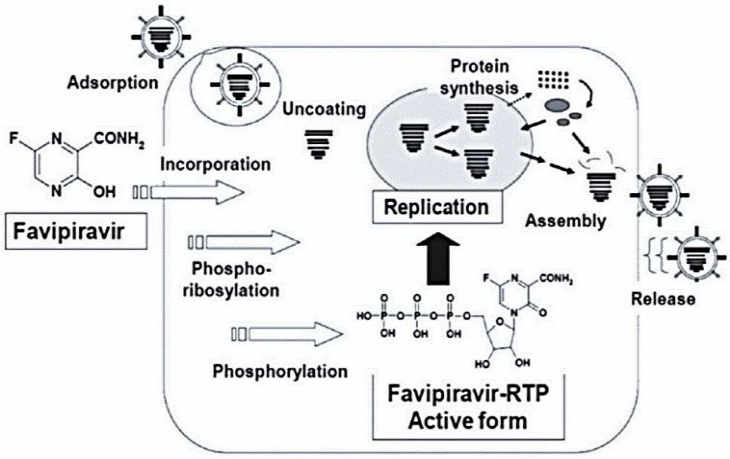


Figure 4

SPECTRUM OF ANTIVIRAL ACTIVITY

A) Influenza: Favipiravir inhibits 53 types of influenza viruses including seasonal strains A (H1N1), A (H3N2), and influenza B; the A (H1N1) pandemic virus; highly pathogenic avian influenza virus A (H5N1) isolated from humans; A (H1N1) and A (H1N2) isolated from swine; and A (H2N2), A (H4N2), and A (H7N2). It is also active against drug-resistant strains of the virus, including M2 and NA inhibitors.[17]

B) Ebola: During the Ebola virus outbreak in 2014, favipiravir was one of the drugs short- listed for trials by the WHO. Although in vitro studies[18, 19] showed encouraging results for this drug, with a trend toward survival benefit showed by clinical studies,[20, 21] conclusive evidence of benefit was never found. In the JIKI multicenter[20] trial 10 conducted in 126 patients with Ebola, favipiravir in an initial loading dose of 6000 mg followed by 2400 mg/day for 9 days was shown to have some effect in patients with medium to high viremia but not in those with more severe viremia (Ct value < 20). This large dose seemed to have been well tolerated as well. A subsequent retrospective study also found favipiravir treated patients had a trend toward improved survival times against Ebola virus, although this effect was not statistically significant.[21]

C) Activity against other pathogenic RNA viruses: In addition to its activity against influenza and Ebola viruses, favipiravir has been found to have therapeutic efficacy in cell culture and mouse models of arena virus, bunya virus, filo virus, West Nile virus, yellow fever virus, foot-and-mouth-disease virus, and Lassa virus including agents causing viral hemorrhagic fevers and encephalitis.

ROLE IN SARS-COV-2

Shannon et al.[22] found that the SARS-CoV-2eRDRp complex is at least 10-fold more active than any other viral RdRp known. Favipiravir acts by inhibiting this viral RdRp enzyme, allowing facile insertion of favipiravir into viral RNA while sparing human DNA. They concluded that nucleoside analogs (such as favipiravir) are promising candidates for the treatment of COVID-19. The optimal dose of favipiravir is difficult to establish from the limited preclinical, in vitro data. For instance, the higher dosing of favipiravir used in Ebola was based on preclinical studies showing the target concentrations needed to inhibit the Ebola virus (EC50: 67 mM) were higher than that in influenza (EC50: 0.48 mM).[23] Despite these high doses, the predicted target concentrations could not be achieved when PK studies were performed on 66 patients in the JIKI trial.[24] Wang et al.[25] found that the high concentrations of favipiravir were needed to inhibit SARS-CoV-2 infection in Vero cells. Thus, it is difficult to ascertain the basis on which the current dose of this drug has been established in SARS-CoV-2.

CLINICAL TRIALS IN COVID-19

Clinical studies have been performed all over the world to assess the efficacy of favipiravir in the management of COVID-19. The Indian clinical studies are summarized here. A randomized, multicenter, open-labeled clinical trial in Indian patients has just been completed, with results expected to be published soon. This trial evaluated the efficacy and safety of favipiravir in patients hospitalized with mild to moderate COVID-19 infection. Conducted in hospitals across India, 150 patients were randomized, with 72 to the favipiravir arm and 75 to the SOC arm. Those in the favipiravir arm received 3600 mg on day 1, then 1600 mg on days 214. Daily nasopharyngeal swabs were collected from all participants till two consecutive swabs were negative. The primary endpoint was time to cessation of shedding of SARS-CoV2 as determined by two consecutive negative swabs. Other secondary endpoints analyzed in this study were clinical cure rates as determined by the treating physician with recovery of fever, respiratory rate, oxygen saturation, and cough relief. The trial also looked

at other secondary endpoints such as time from randomization to initial requirement of high flow supplemental oxygen or ventilator support and time from randomization to hospital discharge. Final data are being analyzed and under review but we can reveal23 that there was 28.7% faster viral clearance in the favipiravir-treated patients compared with those who received SOC (5 versus 7 days) with 2/3rd of favipiravir treated patients achieving viral clearance in week 1. Treating clinicians judged 70% of patients in the favipiravir limb to be clinically cured by day 4 versus 44% in the SOC arm. These initial results were indeed promising but need to be confirmed in larger studies.

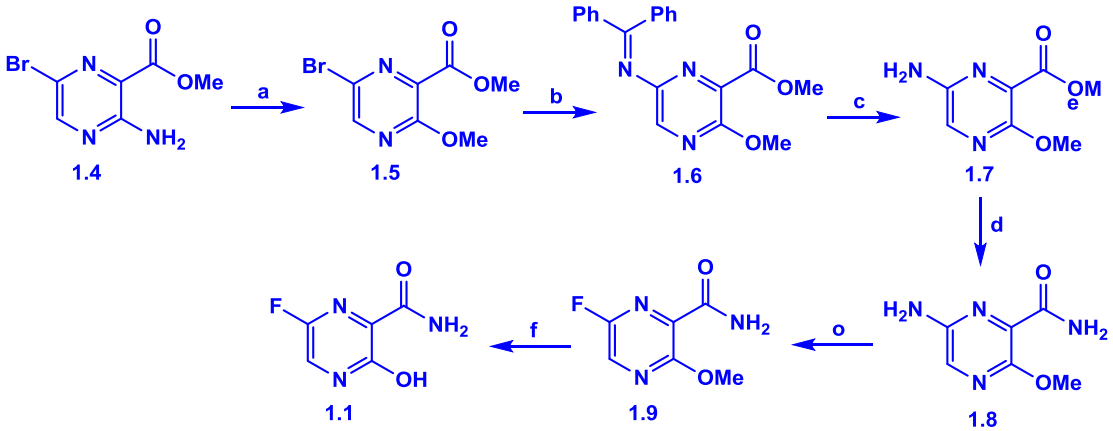
SYNTHESIS OF FAVIPIRAVIR

Favipiravir, with a molecular weight of 157, has been a complicated target to synthesize in spite of its structural simplicity. Favipiravir was first synthesized in 2000, and since then a variety of approaches have been disclosed. Reported synthesis routes to Favipiravir can be divided into two categories, with one group being the routes developed by the innovator Toyama Chemical Company and the other group being routes developed by academia and generic companies.

METHODS DEVELOPMENT BY TOYAMA CHEMICAL COMPANY

METHOD[1]

The first-generation medicinal chemistry route to favipiravir by Toyama Chemical Co. [Scheme 1] comprised six steps with an overall yield of 2% starting from methyl 3-amino-6- bromopyrazine-2-carboxylate (1.4). The synthesis starts with diazotization of 1.4 using conc. sulfuric acid and sodium nitrite followed by addition of MeOH to generate methoxy compound 1.5 in 35% yield. Subsequent cross-coupling of 1.5 with benzophenone imine was carried out using (S)-BINAP generating adduct 1.6, which was then hydrolyzed using 2M HCl to provide 1.7 in 43% yield over two steps. Treating methyl ester 1.7 with methanolic ammonia furnished primary amide 1.8 in 88% yield. Fluorination of 1.8 was accomplished by highly corrosive Olah reagent (sodium nitrite in 70% pyridinium hydro fluoride) with a yield of 86%, furnishing 1.9. The final step involved O-demethylation using in situ generated TMSI to obtain favipiravir in 15% yield.[27-29]



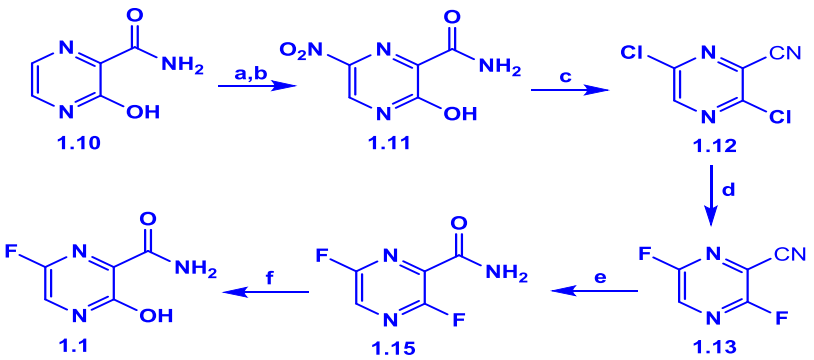
Scheme 1

First generation route to favipiravir by Toyama Chemical Co.

Reagents and conditions: **a)** H_2SO_4, $NaNO_2$, MeOH, reflux, 35%; **b)** diphenylmethanimine, (S)-BINAP, t-BuONa, $Pd_2(dba)_3$, PhMe, 80°C; **c)** 2M HCl, THF, 43% (2- steps); **d)** NH_3, MeOH, 88%; **e)** $NaNO_2$, Pyr-HF, 86%;
f) NaI, TMSCl, MeCN, 15%.

METHOD[2]

The second-generation route[30] developed by Toyama Chemical Company in 2001 was carried out on a multi gram scale [Scheme 2]. The first step involved nitration of 3- hydroxypyrazine-2-carboxamide (1.10) using sodium nitrate in concentrated sulfuric acid, followed by neutralization with aq. NaOH to furnish product 1.11 in 65% yield. Subjecting the nitro compound 1.11 to phosphorus oxychloride and pyridine resulted in the formation of 3,6- dichloropyrazine-2-carbonitrile (1.12) by displacing both the nitro and hydroxyl groups with chlorine atoms along with the dehydration of amide group to nitrile in overall 77% isolated yield. Conversion of compound 1.12 to 3, 6-difluoro-2- carbonitrile (1.13) was achieved in 79% yield using potassium fluoride and tetrabutylammonium bromide in DMSO. The nitrile group of 1.13 was hydrolyzed to amide using 12 M HCl to furnish 3, 6-difluoropyrazine-2- carboxamide (1.15) in 82% yield. The final step included the selective 3-F group hydrolysis. This was accomplished using sodium bicarbonate in dioxane/water resulting in crystalline favipiravir with 52% yield. The synthesis of favipiravir was achieved in 5 steps with an overall yield of 17%, including chromatographic purifications and an allergenic intermediate 1.12.



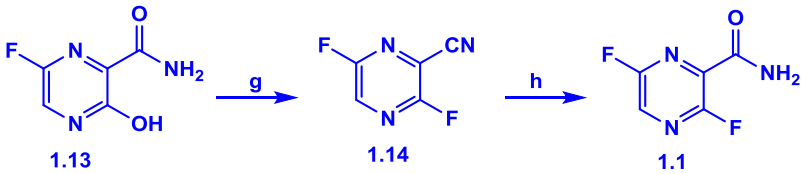
Scheme 2

Second generation route to favipiravir by Toyama Chemical Co.

Reagents and conditions:**a)** $NaNO_3$, Conc. H_2SO_4, 40°C; **b)** aq. NaOH, 65%; **c)** $POCl_3$, pyridine, 100°C, 77%; **d)** KF, TBAB, DMSO, 100°C, 6h, 79%; **e)** 12M HCl, THF, 35°C, 84%; **f)** $NaHCO_3$, dioxane, H_2O, 50°C, 52%.

METHOD[3]

In 2009, Toyama Chemical Co. came up with an alternative route to favipiravir from 3, 6-difluoropyrazine-2-carbonitrile [Scheme 3].[31] This approach involved the selective hydrolysis of the C3 fluoride using potassium acetate in aqueous DMF as the first step. The hydrolysis product 1.14 was purified in 82% yield in the form of a dicyclohexyl ammonium salt, which proved to be the best approach due to the high-water solubility of 1.14. Further hydrolysis of 1.14 with aqueous hydrogen peroxide provided favipiravir in 89% yield after crystallization.

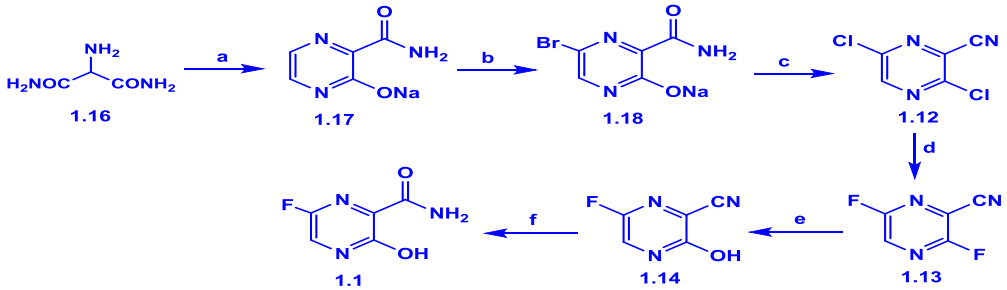


Scheme 3.

Reagents and conditions: **g)** KOAc, DMF, H_2O, 82%; **h)** H_2O_2, H_2O, 89%.

METHOD[4]

Realizing the importance of compound 3, 6-dichloropyrazine-2-carbonitrile (1.12) in the synthesis of favipiravir, Nippon soda[32] developed an improved route starting from 2- aminomalonic acid diamide (1.16) [Scheme 4]. Treating compound 1.16 with glyoxal in aqueous sodium hydroxide solution resulted in the sodium salt of 1.17 in 92% yield, which was crystallized directly from the reaction mixture. Brominating sodium salt of 1.17 with molecular bromine resulted in 1.18 which was crystallized from water in 76% yield. Displacement of bromine and hydroxyl group of 1.18 with chlorine atoms was accomplished using phosphorus oxychloride and DIPEA in chlorobenzene furnishing 3, 6-dichloropyrazine-2-carbonitrile (1.12) in 83% yield. The dichloro compound 1.12 was converted to difluoro compound 1.13 using KF and TBAB in DMSO with 92% yield. Further selective 3-F hydrolysis and nitrile hydrolysis to amide were accomplished using sodium acetate and concentrated sulfuric acid in two steps. This approach establishes a three-step route to 3, 6-dichloropyrazine-2- carbonitrile (1.12), and utilizes the conditions outlined in Scheme 3 to complete the synthesis of favipiravir. Overall yield of the scalable six-step second generation route to favipiravir from compound 1.16 was 33%.

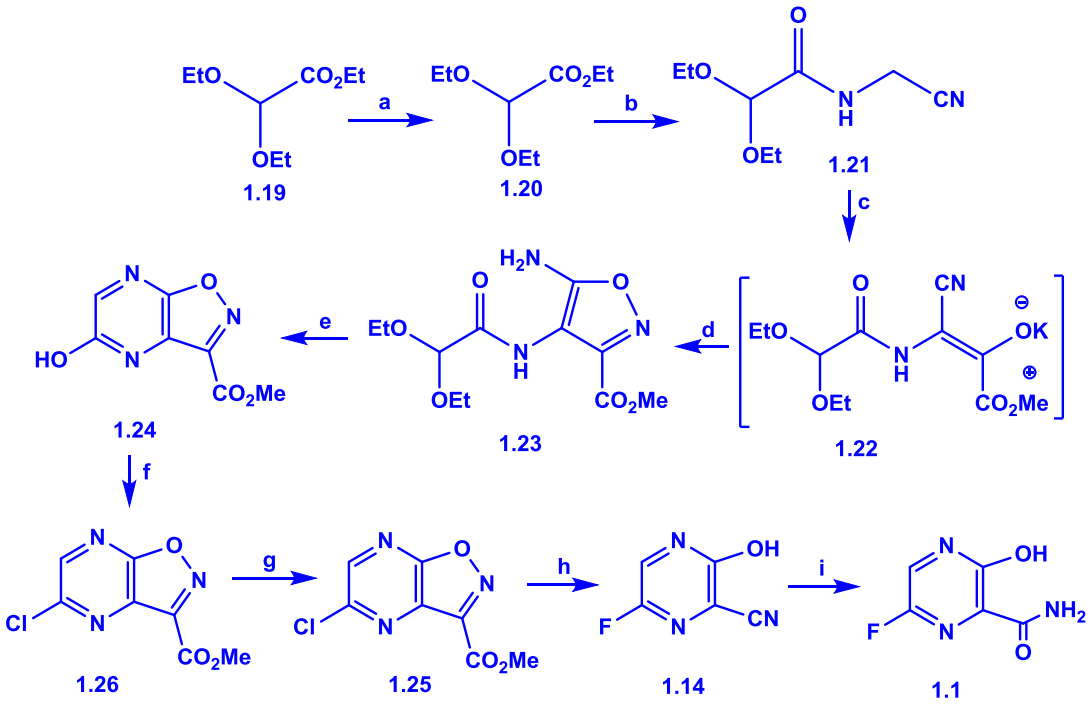


Scheme 4

Scheme 3: Improved route to favipiravir by Nippon Soda. Reagents and conditions: **a)** glyoxal, aq. NaOH, 92%; **b)** Br_2, MeOH/MeCN, 76%; **c)** $POCl_3$, DIPEA, PhCl, 100 °C, 83%; **d)** KF, TBAB, DMSO, 100°C, 6h, 79%; **e)** KOAc, DMF, H_2O, 82%; **f)** H_2O_2, H_2O, 89%.

METHOD [5]

The third-generation route by Toyama Chemical Co. in 2013[33-35] was longer but made use of simple and inexpensive starting materials to make the core pyrazine ring system (Scheme 4). The strategy was to mask the ortho amide and hydroxyl functional groups as an isoxazole. The patent reports the first steps in kilogram scale while final steps were reported in gram scale. Synthesis started by saponification of diethoxyacetate 1.19 to give diethoxyacetic acid (1.20) in 95% yield. The next step involved a CDI mediated acid amine coupling with amino- acetonitrile obtaining product 1.21 in 60% yield. Reaction of 1.21 with dimethyl oxalate with potassium tert-butoxide resulted in intermediate 1.22, which was further treated with hydroxylamine hydrochloride and trifluoroacetic acid to furnish the oxazole 1.23 in 48% yield over two steps. Pyrazine ring was established by hydrolysis of acetal group using p-TSA to generate 1.24 in 58% yield. Replacing the hydroxyl group of 1.24 with a chloride using phosphorus oxychloride and triethyl amine hydrochloride resulted in compound 1.25 in 89% yield. At this stage various esters were synthesized, which gave differing yields in further steps and resulting in ease of operation. The fluorination of 1.25 was carried out with KF in DMSO to yield 1.26 in 84% yield. Addition of 1-chloro-2, 4-dinitrobenzene resulted in cleaner reactions by acting as sink for excess fluorides.

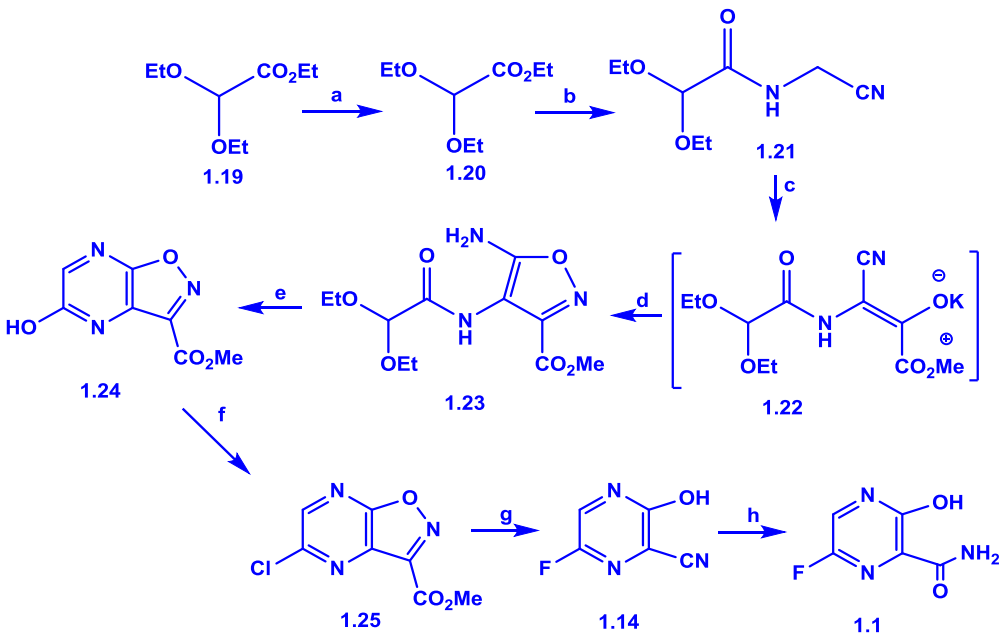


Scheme 5

Third generation route to favipiravir by Toyama Chemical Co. Reagents and conditions: **a)** aq. NaOH, 70°C, 95%; **b)** amino-acetonitrile, CDI, Et3N, MeCN, 60%; **c)** dimethyl oxalate, t-BuOK, THF; **d)** $NH_2OH.HCl$, TFA, MeOH, reflux, 48% (2-steps); **e)** p-TSA-H_2O, AcOH, 77°C, 58%; **f)** $POCl_3$, Et_3N-HCl. 85°C, 89%; **g)** KF, DMSO, 80°C, 84%; **h)** 2,2-difluoro-1,3-dimethylimidazolidine, MeCN, 44%; **i)** NaOH, THF/H_2O, 90%; **j)** NaOH, H_2O_2, 84%.

METHOD [6]

An alternate route where 1.24 was directly converted to the fluorinated compound 1.26 was reported with an isolated yield of 44% by using 2, 2-difluoro-1, 3-dimethylimidazolidine. The final steps include oxazole ring opening with aqueous sodium hydroxide resulting in nitrile 1.14, after purification by an ion-exchange resin. Final hydrolysis of nitrile group was carried out with basic hydrogen peroxide to obtain favipiravir. The authors were able to crystallize favipiravir as its dicyclohexylamine salt resulting in 99.0% pure favipiravir.[34, 35]

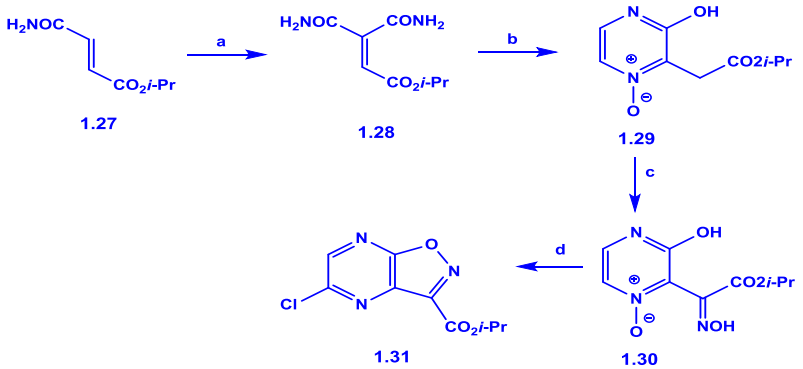


Scheme 6

Third generation route to favipiravir by Toyama Chemical Co. Reagents and conditions: **a)** aq. NaOH, 70°C, 95%; **b)** amino-acetonitrile, CDI, Et_3N, MeCN, 60%; **c)** dimethyl oxalate, t-BuOK, THF; **d)** $NH_2OH.HCl$, TFA, MeOH, reflux, 48% (2-steps); **e)** p-TSA-H_2O, AcOH, 77°C, 58%; **f)** $POCl_3$, Et_3N-HCl. 85°C, 89%; **g)** KF, DMSO, 80°C, 84%; **h)** 2,2-difluoro-1,3-dimethylimidazolidine, MeCN, 44%; **i)** NaOH, THF/H_2O, 90%; **j)** NaOH, H_2O_2, 84%.

METHOD [7]

Toyama Chemical Co.[33-35] also reported a four-step synthetic route to intermediate 1.31 using maleic amide-ester 1.27 as the starting material [Scheme 7]. Ester-amide 1.28 was obtained by Michael addition of hydroxylamine to 1.27 in aqueous isopropanol with an isolated yield of 59% after crystallization. Condensation of 1.28 using aqueous glyoxal solution along with sodium carbonate solution resulted in pyrazine N-oxide 1.29 in 62% yield after crystallization. The N-oxide 1.29 was further converted to oxime 1.30 using isoamyl nitrite and acetyl chloride with an 88% yield after crystallization from reaction mixture. Final step involving the ring closure and chlorination was accomplished on treatment of 1.30 with phosphorus oxychloride affording isopropyl ester 1.31 in 49% yield. Although the yields have been moderate in most of the steps, the advantage is in the isolation of products. All the products are crystalline, and several products were directly crystallized from the reaction mixture.



Scheme 7

Alternate route to intermediate 1.31 by Toyama Chemical Co.18–20. Reagents and conditions.
a) aq. NH_2OH, i-PrOH, 59%; **b)** glyoxal, aq. Na_2CO_3, i-PrOH, 41°C, 62%; **c)** isoamyl nitrite, CH_3COCl, i-PrOH, 88%; **d)** $POCl_3$, PhMe/DMF, 70°C, 49%.

The first-generation route focused mainly on obtaining small quantities of compound for various screening studies and initial testing. Unfortunately, this was not appropriate for scaling up due to the use of highly corrosive reagents, expensive catalysts, and purification hurdles. The second-generation route provided a six-step

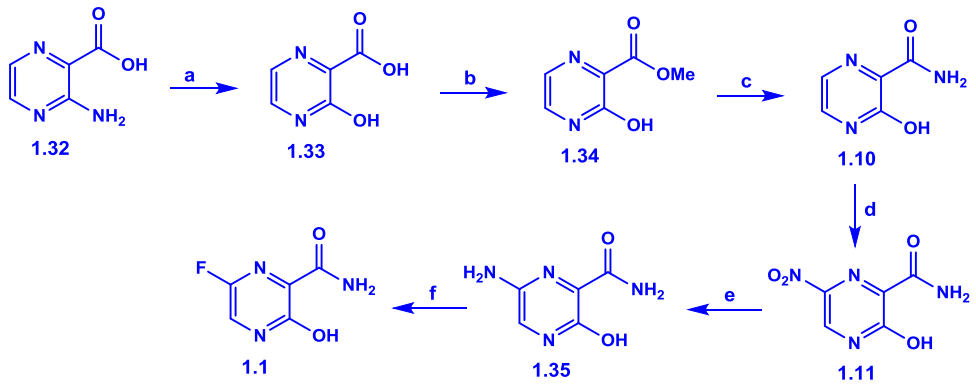
scalable route to favipiravir owing to the contributions from both Toyama Chemical Co.[30, 31] and Nippon Soda.[32] The overall yield of favipiravir has been increased to 33% on a scale as compared to the first-generation route. The Nippon Soda route provides a short and scalable route to 3, 6-dichloropyrazine-2-carbonitrile (1.12) from inexpensive and commercially available diamide 1.16 in three-steps. This was followed by Toyama Chemical Co. route (1.12 → 1.13 → 1.14 → 1.1, Scheme 2) which involves purification of intermediate 1.14 as a dicyclohexylamine salt. The only drawback of this route was the late-stage intermediate 3, 6-difluoropyrazine-2-carbonitrile (1.13), which was reported to be volatile and have high skin irritancy requiring special equipment and handling techniques. The third-generation route has an overall yield of 9% with nine-steps (Scheme 6) or 10% (Scheme 6 & Scheme 7). Due to modest yields and length of the synthesis, this has not been an attractive route to synthesize favipiravir. Most of the compounds reported were liquids and required vacuum distillation. This approach has an advantage from the safety point of view. It skips the difluoro intermediate 1.13 reported to be volatile and a skin irritant, thereby eliminating the need for special equipment.

METHODS DEVELOPED BY ACADEMIC LABORATORIES AND GENERIC COMPANIES

A variety of synthetic routes have been developed by generic companies and academic laboratories all over the world.

METHOD [8]

In 2012, Zhang and co-workers from Shandong Qidu Pharmaceutical company patented a short route to favipiravir starting from 3-aminopyrazine-2- carboxylic acid (1.32) (Scheme 8).[36] Nitration of 1.10 as described in Scheme 6 gave the nitro compound 1.11 in 76% yield. Hydrogenation of 1.11 over Pd/C gave the corresponding amine 1.35 in 65% yield after crystallization. Treatment of amine 1.35 with 70% pyridinium hydro fluoride and sodium nitrite furnished favipiravir in 70% yield after an aqueous workup. No information regarding the purity of favipiravir was mentioned and the three-step route from 1.10 to favipiravir had an overall yield of 34%.

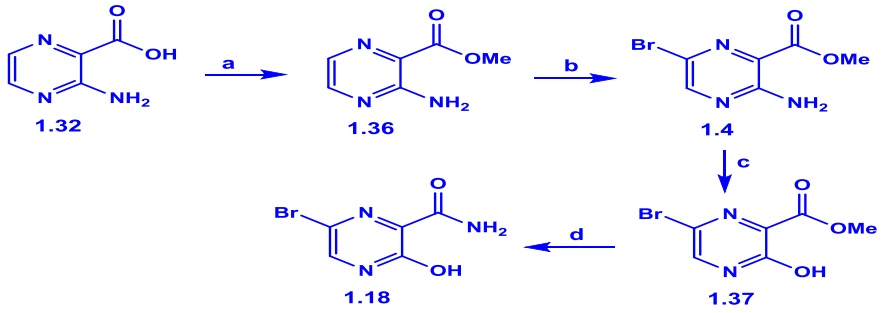


Scheme 8

Synthesis route to favipiravir by Zhang and co-workers. Reagents and conditions: **a)** 1 M HCl, $NaNO_2$, 0°C, 90%; **b)** H_2SO_4, MeOH, 40°C, 92%; **c)** $NH_3.H_2O$, MeOH, rt, 95%; **d)** H_2SO_4, HNO_3, -5°C, 76%; **e)** H_2, 5% Pd/C, AcOH, 10°C, 65%; **f)** $NaNO_2$, Pyr-HF, -20°C, 70%.

METHOD [9]

A route from Zhang and co-workers in year 2013 (Scheme 9)[37] arrives at the intermediate 1.18 of Nippon Soda synthesis (Scheme 5) starting from 3-amino-2-pyrazinecarboxylic acid (1.32). Esterification of 1.32 was followed by bromination using NBS, diazotization, hydrolysis and amide formation resulted in the required intermediate 1.18.



Scheme 9.

Route to intermediate 1.18 by Zhang and co–workers. Reagents and conditions: **a)** H_2SO_4, MeOH, 0°C, 8h, 70%; **b)** NBS, MeCN, rt, 24h, 87%; **c)** H_2SO_4, $NaNO_2$, H_2O, rt, 2h, 93%; **d)** $NH_3.H_2O$, rt, 3h, 94%.

SIDE EFFECTS/ADVERSE EFFECTS

The study[38] discussed previously found that adverse reactions were seen in around 20% of the patients who received favipiravir (at a dose lower than approved for COVID-19). The adverse effects were relatively minor and included hyperuricemia and diarrhea in 5% of the participants and reduced neutrophil count and transaminitis in 2% of the participants. One study showed occurrence of psychiatric symptoms in association with favipiravir. Effect of favipiravir in QTc prolongation is still uncertain, with some pharmacodynamic studies suggesting a positive association, but a Japanese study suggesting otherwise. Overall, favipiravir has a good safety profile, as was confirmed by a large systematic review. In the following sections, we give a brief overview of the adverse effect profile of this drug.

Hyperuricemia: The prevalence of hyperuricemia shows an increasing trend that is dose- dependent with the use of Favipiravir, according to a systematic review conducted by Pilkington et al. Several studies have shown similar trends. Nevertheless, there seems to be no correlation between hyperuricemia caused by Favipiravir and clinical manifestations. Although, to fully evaluate this risk, longer follow-up periods would be necessary.

Teratogenicity: According to the Japanese drug safety bureau approval, there is evidence that Favipiravir exhibits embryo toxicity and has the potential to be teratogenic. As a result, the bureau advises that women of reproductive age be strongly warned against the use of Favipiravir and recommends that precautionary statements be included on packaging and prescription alerts. Additionally, the bureau suggests avoiding the use of Favipiravir where alternative drugs could be used. Men who have received treatment with Favipiravir should be instructed to use effective contraceptive methods during and for 7 days after treatment. Before prescribing Favipiravir to women of child-bearing age, it is essential to confirm the absence of pregnancy by performing a negative urine pregnancy test.[39-41]

DRUG INTERACTIONS

PYRAZINAMIDE

Concomitant use of pyrazinamide with favipiravir increases the levels of uric acid. Regular uric acid level monitoring is mandatory when these drugs are used together.

REPAGLINIDE

Favipiravir inhibits the metabolism of repaglinide through the CYP2C8 pathway, thus increasing its potential to cause toxicity (hypoglycemia, headache, increase incidence of upper respiratory tract infections, etc.). Cautious concomitant use is recommended.

THEOPHYLLINE

Theophylline increases the blood levels of favipiravir and adverse reactions to favipiravir may occur.

FAMCICLOVIR, SULINDAC

Efficacy of these drugs may be reduced when co-administered with favipiravir.

ACYCLOVIR

Acyclovir may delay the conversion of favipiravir into the active moiety, thus reducing its antiviral efficacy.[42]

CONCLUSION

Since Favipiravir possess a wide spectrum of Antiviral activities against SARS-COV-2, Influenza and other RNA polymerase viruses and also interacts with other drugs and modify their efficacy, a number of methods have been developed from time to time for the synthesis by TOYAMA company, other academia and generic companies. Here efforts are made to compile most of these methods that have been reported in the literature. This review will be very useful for the researchers working in this field, and it would help them to develop a new eco-friendly, efficient and economical method for synthesis of favipiravir. This is necessary from today's point of view as we need an environmentally clean protocol for the large scale production of such a crucial biological moiety.

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