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MONOGRAPH

FAVIPIRAVIR

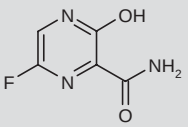
Rec INN

RNA-Directed RNA Polymerase NS5B Inhibitor
Treatment of Influenza A

T-705

6-Fluoro-3-hydroxypyrazine-2-carboxamide

InChI: 1S/C5H4FN3O2/c6-2-1-8-5(11)3(9-2)4(7)10/h1H,(H2,7,10)(H,8,11)



$C_5H_4FN_3O_2$
Mol wt: 157.1026
CAS: 259793-96-9
EN: 286877

SUMMARY

Influenza is an extremely contagious disease caused by infection with influenza viruses. So far, available treatment includes two types of drugs: M2 ion channel inhibitors and neuraminidase inhibitors (NAIs). Vaccines are also available for prophylaxis. Influenza viruses are able to undergo rapid antigenic changes, and novel influenza virus variants with high levels of virulence may emerge and cause severe disease. Furthermore, antiviral resistance and limited antiviral efficacy in severe cases of influenza have been reported. Therefore, the search for alternative anti-influenza virus agents is of utmost importance. Favipiravir (T-705) is a unique viral RNA polymerase inhibitor, acting on viral genetic copying to prevent its reproduction. It is a broad-spectrum antiviral agent that has potent inhibitory activity against RNA viruses in cell culture, especially influenza A, B and C viruses, whereas it showed no cytotoxicity even at high concentrations. Animal studies have further verified the antiviral activity of favipiravir against influenza viruses, as well as the Flaviviridae, Bunyaviridae and Arenaviridae families of viruses.

C. Reviriego. UCD Conway Institute of Biomolecular and Biomedical Research, School of Medicine and Medical Science, University College Dublin, Belfield, Dublin 4, Dublin, Ireland. E-mail: carlota.reviriego@gmail.com.

*Synthesis prepared by R. Castañer. Thomson Reuters, Provença 388, 08025 Barcelona, Spain.

SYNTHESIS*

Treatment of methyl 6-bromo-3-amino-2-pyrazinecarboxylate (I) with sodium nitrite ($NaNO_2$) in H_2SO_4 followed by refluxing in MeOH yields methyl 6-bromo-3-methoxy-2-pyrazinecarboxylate (II), wherein the Br group is converted to an amino functionality by treatment with benzophenone imine, tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_2$] (*S*)-(–)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and sodium *tert*-butoxide in toluene, and finally with HCl in THF, affording methyl 6-amino-3-methoxy-2-pyrazinecarboxylate (III). Treatment of methyl ester (III) with ammonia gas in MeOH gives the carboxamide (IV), which is then treated with pyridine hydrofluoride and $NaNO_2$ to give 6-fluoro-3-methoxy-2-pyrazinecarboxamide (V). Finally, compound (V) is demethylated by reaction with NaI and trimethylsilyl chloride (TMSCl) in acetonitrile (1). Scheme 1.

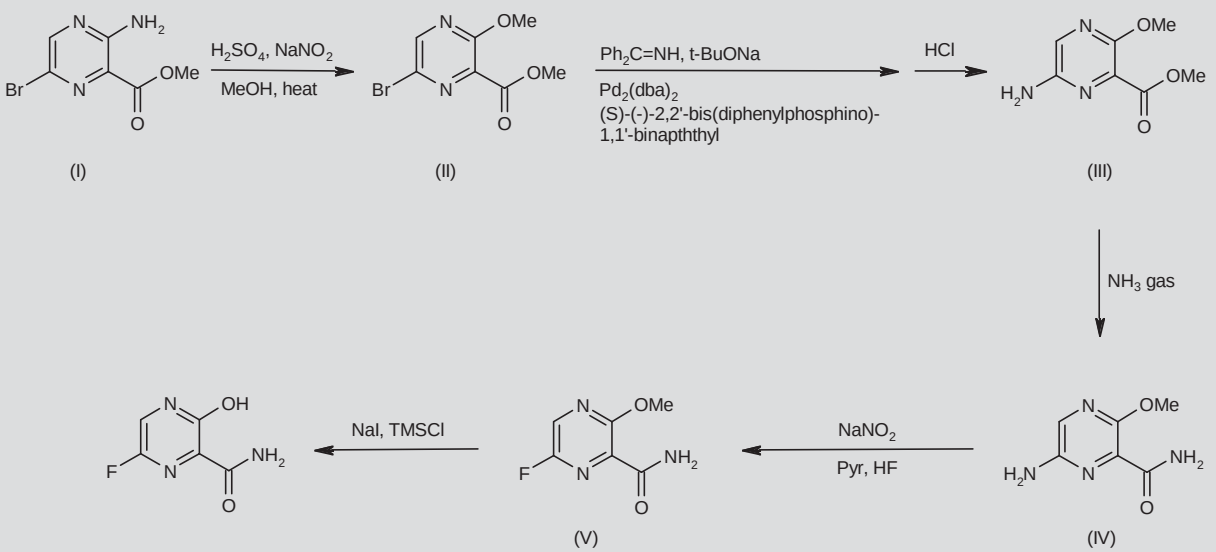
Alternatively, regioselective fluoride group substitution in 3,6-difluoropyrazine-2-carbonitrile (VI) using KOAc in the presence of NH_4OH leads to the corresponding 3-hydroxypyrazine derivative (VII), isolated as the dicyclohexylamine salt by treatment with DCHA in DMF/H_2O. Finally, nitrile (VII) is hydrolyzed using $NaOH/H_2O_2$ followed by treatment with HCl (2). Scheme 2.

BACKGROUND

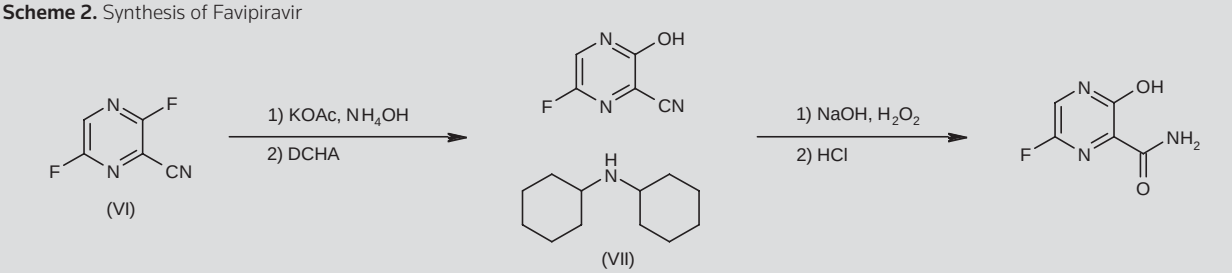
Influenza is one of the oldest and most common infections, causing significant morbidity and mortality. Influenza viruses infect the respiratory tract and are highly pathogenic for humans. The illness can cause severe complications, including pneumonia and ischemic heart disease, and can lead to hospitalization, and ultimately death, in groups such as young children, the elderly and immunocompromised patients (3, 4). Vaccination and treatment with antivirals are both available to control human influenza. Although vaccination plays a critical role in influenza prophylaxis (5), it is not enough, especially against pandemic virus.

Currently, two classes of anti-influenza drugs are available for the treatment and management of this disease: M2 ion channel blockers (also known as adamantanes) and neuraminidase inhibitors (NAIs). The use of M2 channel blocker-type drugs is limited due to the rapid emergence of transmissible drug-resistant mutant viruses, and the fact that they only offer protection against influenza A viruses (6). These drugs inhibit viral fusion and uncoating by binding to

Scheme 1. Synthesis of Favipiravir



Scheme 2. Synthesis of Favipiravir



the viral M2 protein, which is not encoded by influenza B and C viruses (7).

NAIs have specific inhibitory activity against viral neuraminidase, one of the major surface glycoproteins, which is expressed by both influenza A and B viruses (8, 9). Therefore, these drugs are active against influenza A and B viruses, but not against influenza C viruses (10). Two NAIs, zanamivir and oseltamivir, are licensed for use. Oseltamivir is the predominant choice, and is used worldwide for the treatment of influenza. However, the generation and circulation of oseltamivir-resistant seasonal influenza viruses has recently increased (11, 12). Currently, zanamivir is the only drug effective against both adamantane-resistant and/or oseltamivir-resistant influenza viruses, but due to the fact that it has to be inhaled, it is less suitable for use by several high-risk groups (13, 14). Collectively, these findings emphasize not only the need for effective new antivirals, but also the need to identify new molecular targets (15).

Favipiravir (T-705), a novel pyrazine derivative, is orally active against influenza viruses, including H5N1 avian influenza and H1N1 infections, in both cell culture and animal models (16). It has been reported to be broadly effective against other RNA viruses, namely arenaviruses, bunyaviruses and flaviviruses, in mouse and/or hamster infection models (17-19). Favipiravir has shown no cytotoxicity and strong therapeutic efficacy in lethal infection models in mice (20, 21). In fact, it affects the synthesis of influenza viral RNA, but not cellular DNA or RNA (16). Favipiravir has also been found to be synergistically effective when used with another influenza virus inhibitor with a different mechanism of action, such as oseltamivir (22, 23).

Although further investigation is necessary, the overall findings strongly indicate the potential for favipiravir to be used therapeutically for the control of influenza virus infections, either alone or in combination with oseltamivir (22). It may also be of potential utility in the treatment of other diseases, such as yellow fever virus disease

(19), West Nile virus infection (18) or hemorrhagic fever caused by RNA viruses (17).

PRECLINICAL PHARMACOLOGY

In vitro favipiravir was effective against several H5N1 strains. Efficacy was generally stronger than that displayed by the guanosine analogue ribavirin, but considerably less compared to oseltamivir and zanamivir (21). Favipiravir was also found to be highly effective against multiple strains of drug-sensitive and -resistant seasonal influenza isolates, as well as avian A (H5N1) and the 2009 A (H1N1) pandemic strains (24). In fact, while oseltamivir only inhibited influenza A and B viruses, favipiravir showed potent inhibitory activity against all types of influenza A, B and C viruses (20). However, it has been reported that favipiravir did not exert any antiviral activity when added 1 h before or 6-10 h after infection with H1N1 (16). Favipiravir did not inhibit herpes simplex virus type 1 (HSV-1), human cytomegalovirus or adenovirus, but poliovirus, rhinovirus and respiratory syncytial virus were slightly susceptible. Favipiravir showed no cytotoxicity against mammalian cell lines at concentrations up to 1000 µg/mL (20).

In vivo favipiravir was significantly more effective than oseltamivir against H1N1 (25) and H5N1 (21) viruses. Although 5 days of treatment with favipiravir at 300 mg/kg/day was almost as effective as oseltamivir against highly pathogenic H5N1 viruses in mice, enhanced efficacy with favipiravir was observed on an 8-day regimen (26). Moreover, regardless of the infecting virus strain, including wild-type and oseltamivir-resistant mutants, the number of surviving animals increased dose-dependently with orally administered favipiravir (20, 26). In contrast, oseltamivir phosphate, the active form of oseltamivir, exhibited limited efficacy against oseltamivir-resistant mutants (26). Doses of favipiravir of 200 mg/kg/day for 5 days significantly protected the mice from death, while a lower dose also had a significant therapeutic effect in terms of survival rates (20). When favipiravir was administered at 1, 24, 48 and 72 h postinfection at 300 mg/kg/day, mice were completely protected from lethal virus infection, whereas oseltamivir only protected 50% of the mice at best (26). Similar results were obtained against H1N1 (25). However, other authors have reported that only a higher dose (600 mg/kg/day) provided protection when treatment was started 60 h postinfection (21).

Favipiravir has also been tested against other RNA viruses. It was moderately active against yellow fever virus in cell culture (19). The same authors observed that the antiviral activity of favipiravir occurs at late stages of virus replication (19), in agreement with previously published data involving time-of-addition studies (16). Favipiravir has also been found to be effective against bunyaviruses (17, 27-29), and was even more potent against arenaviruses (17, 28), as well as West Nile virus (18) and Western equine encephalitis (30).

Hamsters treated with favipiravir at doses of 200 and 400 mg/kg/day showed significant protection from death caused by yellow fever virus when compared to the placebo-treated controls, although T-1106, a chemically similar compound, exhibited superior activity (19, 31). Similar results were observed in a Punta Toro virus infection model in hamsters. However, the greater efficacy exhibited in the hamster system was not apparent in mice (27). Strong activity for favipiravir was observed in mice and hamsters against Punta Toro virus infections (17, 28), but its toxicity was greater in mice than in hamsters (17).

Favipiravir protected against Pichinde virus in hamsters (28, 32, 33). In fact, it was effective when administered early during the course of infection, after the animals became ill and the day before the animals began to succumb to the disease (32). Lower doses of ribavirin were more effective than favipiravir for the treatment of Pichinde virus infection in hamsters, but considering the toxicity of ribavirin and the lack of toxicity with favipiravir, the latter may be a viable alternative for arenavirus disease (17). Favipiravir was more effective than T-1106 against Pichinde virus (27, 33).

Orally administered favipiravir was effective against West Nile virus and Western equine encephalitis virus infections in both mice and hamsters (18, 30), improving survival of the animals.

The combination of favipiravir and oseltamivir at high doses was highly synergistic in mice and the use of favipiravir may permit the use of lower doses of oseltamivir to achieve efficacy against H1N1 viruses (23). Similar results were observed against H3N2 and H5N1 (22). There was no evidence of synergy with the combined therapy employing a limited amount of suboptimal doses of ribavirin and favipiravir with treatments initiated 5 days after Pichinde virus challenge (32). In contrast, greater activity was observed when favipiravir was combined with ribavirin in the treatment of hamsters infected with yellow fever virus compared to monotherapies (31).

PHARMACOKINETICS AND METABOLISM

Pharmacokinetic analysis of favipiravir indicated that only 10% of the drug remains 6 h following a single oral dose in mice (17). Plasma drug levels following oral administration are markedly reduced during the latter stages of Pichinde virus disease in hamsters (32).

Both single- and multiple-dose, randomized, double-blind, placebo-controlled, ascending-dose studies have been conducted in healthy male volunteers. In the single-dose trial, favipiravir was characterized by rapid absorption and elimination in urine as M1, the major metabolite. The maximum plasma concentration (C_{max}) increased proportionally to dose. In the multiple-dose study, the plasma concentrations increased progressively due to inhibition of metabolic enzymes (34).

Although no in vivo studies have been performed, the favorable intracellular metabolic properties of favipiravir combined with its reduced cell-inhibitory properties make this compound an attractive candidate for treating human influenza virus (35).

SAFETY

Favipiravir appeared to be well tolerated in mice, with no deaths and no weight loss during treatment (18, 21), and no toxicity was seen in hamsters (17). The compound has been well tolerated as both single and multiple doses in healthy volunteers, with no serious adverse events reported (34).

CLINICAL STUDIES

A phase I clinical study was conducted in healthy adult male volunteers to determine the safety, tolerability and pharmacokinetics in

humans (34). A phase III study in infected patients was initiated in October 2009 (36). The primary objective of this study was to demonstrate the noninferiority of favipiravir compared to oseltamivir phosphate. A phase II study in an older population with uncomplicated influenza was set to begin in early 2010 (37). The aim of the trial was to evaluate the clinical efficacy of two dose regimens of favipiravir compared with placebo in treating the enrolled patients. No results have been published to date.

SOURCE

Toyama Chemical Co., Ltd. (JP).

DISCLOSURES

The author states no conflicts of interest.

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