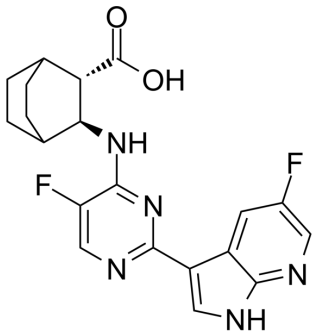
Pimodivir



Cat. No.:	HY-12353A
CAS No.:	1629869-44-8
Molecular Formula:	$C_{20}H_{19}F_2N_5O_2$
Molecular Weight:	399.39
Target:	Influenza Virus
Pathway:	Anti-infection
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year

SOLVENT & SOLUBILITY

In Vitro

DMSO : 5 mg/mL (12.52 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5038 mL	12.5191 mL	25.0382 mL
	5 mM	0.5008 mL	2.5038 mL	5.0076 mL
	10 mM	0.2504 mL	1.2519 mL	2.5038 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.26 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.26 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.26 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pimodivir (VX-787) is an orally bioavailable inhibitor of influenza A virus polymerases through interaction with the viral PB2 subunit.

In Vitro

Pimodivir rescues macrophages from virus-mediated death at non-cytotoxic concentrations 24 hpi. The EC_{50} value for Pimodivir are 8 and 12 nM for A(H1N1) and A(H3N2) strains, respectively, whereas the CC_{50} values are >1 μM, giving selectivity indexes (SI) > 125 and > 83 for A(H1N1) and A(H3N2) strains, respectively. Pimodivir significantly attenuates the transcription of viral M1 RNA in macrophages, which are infected with A(H1N1) or A(H3N2) strains for 8 h. Pimodivir inhibits

	the transcription of viral but not cellular genes. Pimodivir allows some activation of IAV-mediated expression of several cellular genes, which are involved in tryptophan and nucleotide metabolism. Pimodivir possesses excellent anti-IAV but not immuno/metabolo-modulating effect[2]. Pimodivir (VX-787) is very potent against influenza A strains, including pandemic 2009 H1N1 and avian H5N1[3]. Pimodivir (VX-787) shows potent activity against all influenza A virus strains tested, with an EC_{50} range of 0.13 to 3.2 nM. Pimodivir-selected PB2 variant viruses maintain susceptibility to neuraminidase inhibitors in vitro [4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Pimodivir (2, 6, and 20 mg/kg/day, p.o.) and GS 4071 (20 mg/kg/day) completely prevent death in the H1N1pdm virus infection in mice. Pimodivir (20 mg/kg/day) is more effective than GS 4071 (20 mg/kg/day) in improving body weight and reducing the severity of lung infection[1]. Moreover, Pimodivir (VX-787) shows 100% survival in a +48 h delay to treatment mouse influenza model at 10, 3 and 1 mpk (BID × 10 days) whereas the SOC, GS 4071, provide no survival benefit in this model at 10 mpk[3]. Pimodivir (VX-787; 1, 3, or 10 mg/kg, bid) provided complete survival, with a dose-dependent reduction in BW loss of the mice[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	The compound cytotoxicity and efficacy testing is performed in 96-well plates with macrophages at 95% confluence. The compounds are added to the medium, and 30 min later, the cells are infected with virus or non-infected. The cell viability is analyzed with the Cell Titer Glo assay at 24 hpi. The luminescence is read with a PHERAstar FS plate reader. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	The mice are anesthetized, and the animals are infected intranasally with a 90-µL suspension of influenza virus. The virus challenge is approximately four 50% mouse lethal infectious doses. Treatments are given twice a day (at 12 h intervals) for 10 days starting 2 h before virus challenge. Parameters for assessing the infection are survival, mean day of death, body weight changes, and lung infection parameters (hemorrhage score, weight, and virus titer). Animals are weighed individually every other day through day 21 of the infection. Initially, there are 15 mice per group treated with compound and 25 placebos. Five mice in each group are subsequently sacrificed for determination of lung infection parameters. A larger number of placebos are used than compound-treated mice to achieve greater statistical power, especially if some animals in that group survive the infection. One mouse that dies during the treatment period is presumed to have died from treatment trauma because its death occurs well before other mice die from influenza. It is excluded from the total counts. Animals that die during infection are accounted for in the tabular data. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nucleic Acids Res. 2018 Jan 25;46(2):956-971.
- Antiviral Res. 2021 Feb 10;188:105035.
- bioRxiv. 2021 Jan 5.

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REFERENCES

[1]. Smee DF, et al. Activities of JNJ63623872 and GS 4071 against influenza A H1N1pdm and H3N2 virus infections in mice. Antiviral Res. 2016 Dec;136:45-50.

[2]. Fu Y, et al. JNJ872 inhibits influenza A virus replication without altering cellular antiviral responses. Antiviral Res. 2016 Sep;133:23-31.

[3]. Boyd MJ, et al. Isosteric replacements of the carboxylic acid of drug candidate VX-787: Effect of charge on antiviral potency and kinase activity of azaindole-based influenza PB2 inhibitors. Bioorg Med Chem Lett. 2015 May 1;25(9):1990-4.

[4]. Byrn RA, et al. Preclinical activity of VX-787, a first-in-class, orally bioavailable inhibitor of the influenza virus polymerase PB2 subunit. Antimicrob Agents Chemother. 2015 Mar;59(3):1569-82.

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