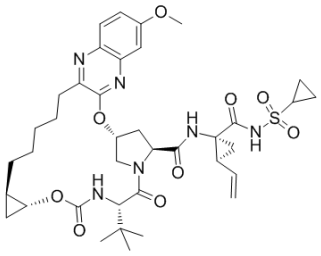
Grazoprevir

Cat. No.:	HY-15298
CAS No.:	1350514-68-9
Molecular Formula:	$C_{38}H_{50}N_6O_9S$
Molecular Weight:	766.9
Target:	HCV Protease; HCV; SARS-CoV
Pathway:	Anti-infection; Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (65.20 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.3040 mL	6.5198 mL	13.0395 mL
	5 mM	0.2608 mL	1.3040 mL	2.6079 mL
	10 mM	0.1304 mL	0.6520 mL	1.3040 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 (3.26 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.26 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Grazoprevir (MK-5172) is a selective inhibitor of Hepatitis C virus NS3/4a protease with broad activity across genotypes and resistant variants, with K_is of 0.01 nM (gt1b), 0.01 nM (gt1a), 0.08 nM (gt2a), 0.15 nM (gt2b), 0.90 nM (gt3a), respectively[1][2]. Grazoprevir inhibits SARS-CoV-2 $3CL^{pro}$ activity[3].

IC_{50} & Target

Ki: 0.01±<0.01 nM (gt1b), 0.01±0.01 nM (gt1a), 0.08±0.02 nM (gt2a), 0.15±0.06 nM (gt2b), 0.90±0.2 nM (gt3a)[1]

In Vitro

In biochemical assays, Grazoprevir (MK-5172) is effective against a panel of major genotypes and variants engineered with common resistant mutations, with K_i of 0.01±<0.01 nM (gt1b), 0.01±0.01 nM (gt1a), 0.08±0.02 nM (gt2a), 0.15±0.06 nM (gt2b), 0.90±0.2 nM (gt3a), 0.07±0.01 nM ($gt1b^{R155K}$), 0.14±0.03 nM ($gt1b^{D168V}$), 0.30±0.04 nM ($gt1b^{D168Y}$), 5.3±0.9 nM ($gt1b^{A156T}$), and 12±2 nM ($gt1b^{A156V}$), respectively. In the replicon assay, Grazoprevir demonstrates subnanomolar to low-nanomolar EC_{50}s

	against genotypes 1a, 1b, and 2a, with EC_{50}s of 0.5±0.1 nM, 2±1 nM, and 2±1 nM for gt1b^{con1}, gt1a, and gt2a, respectively. Grazoprevir is potent against a panel of HCV replication mutants NS5A (Y93H) (EC_{50}=0.7±0.3 nM), NS5B nucleosides (S282T) (EC_{50}=0.3±0.1 nM), and NS5B (C316Y) (EC_{50}=0.4±0.2)[1]. Grazoprevir (MK-5172) maintains the excellent potency against the gt 3a enzyme as well as a broad panel of mutant enzymes, has excellent potency in the replicon system [gt1b IC_{50}(50% NHS)=7.4 nM; gt1a IC_{50}(40% NHS)=7 nM], and shows excellent rat liver exposure[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Grazoprevir (MK-5172) demonstrates efficacy in vivo against chronic-HCV-infected chimpanzees[1]. When dosed to dogs, Grazoprevir (MK-5172) shows low clearance of 5 mL/min/kg and a 3 h half-life after iv dosing and has good plasma exposure (AUC=0.4 μM h) after a 1 mg/kg oral dose. Dog liver biopsy studies showed that the liver concentration of Grazoprevir after the 1 mg/kg oral dose is 1.4 μM at the 24 h time point. Similar to its behavior in rats, Grazoprevir demonstrates effective partitioning into liver tissue and maintains high liver concentration, relative to potency, 24 h after oral dosing in dogs[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Rats and Dogs[1] Studies are performed in both rats and dogs. For studies in which Grazoprevir is dosed intravenously to rats or dogs, the compound is formulated in polyethylene glycol 200 (PEG200) and administered as a bolus at either 2 mg/kg of body weight (Rats) or 0.5 mg/kg (dog). For oral studies, the crystalline potassium salt of the compound is dosed as a solution in PEG400 at 5 mg/kg (Rats) or 1 mg/kg (dog). For all studies, blood samples are collected in EDTA-containing tubes at appropriate times and plasma is separated by centrifugation and stored at −70°C until analysis. Quantitation of Grazoprevir (MK-5172) levels is conducted by high-performance liquid chromatography/mass spectroscopy (LC/MS/MS) following protein precipitation. Liver samples are obtained from rat studies at the termination of the experiment. For dog, liver biopsy samples (20 μL) are collected following sedation. Tissue samples are homogenized in four volumes of deionized water, and drug concentrations are determined by LC/MS/MS after protein precipitation. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Biotechnol. 2019 Oct;37(10):1209-1216.
- Nat Methods. 2018 Jul;15(7):519-522.
- Signal Transduct Target Ther. 2021 May 29;6(1):212.
- Nat Commun. 2020 Sep 4;11(1):4417.
- Elife. 2020 Jun 9;9:e56469.

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REFERENCES

[1]. Summa V, et al. MK-5172, a selective inhibitor of hepatitis C virus NS3/4a protease with broad activity across genotypes and resistant variants. Antimicrob Agents Chemother. 2012 Aug;56(8):4161-7.

[2]. Harper S, et al. Discovery of MK-5172, a Macrocyclic Hepatitis C Virus NS3/4a Protease Inhibitor. ACS Med Chem Lett. 2012 Mar 2;3(4):332-6.

[3]. Qi Sun, et al. Bardoxolone and bardoxolone methyl, two Nrf2 activators in clinical trials, inhibit SARS-CoV-2 replication and its 3C-like protease. Signal Transduct Target Ther. 2021 May 29;6(1):212.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA