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产品名称：MK-5172
产品别名：Grazoprevir；格佐匹韦

生物活性：

Description	Grazoprevir (MK-5172) is a selective inhibitor of Hepatitis C virus NS3/4a protease with broad activity across genotypes and resistant variants, with Kis of 0.01 nM (gt1b), 0.01 nM (gt1a), 0.08 nM (gt2a), 0.15 nM (gt2b), 0.90 nM (gt3a), respectively.
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].
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].

In Vitro:

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

H_2O : < 0.1 mg/mL (insoluble)

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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

Solvent&Solubility	——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (3.26 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.26 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (3.26 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.26 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Animal Administration	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.
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.