Telaprevir

Cat. No.: HY-10235

CAS No.: 402957-28-2

Molecular Formula: $C_{36}H_{53}N_7O_6$

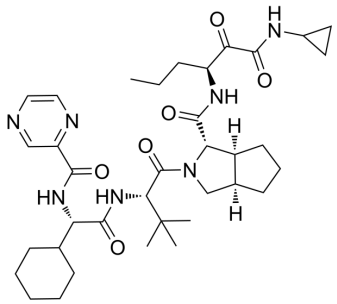
Molecular Weight: 680

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	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 50 mg/mL (73.53 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.4706 mL	7.3529 mL	14.7059 mL
	5 mM	0.2941 mL	1.4706 mL	2.9412 mL
	10 mM	0.1471 mL	0.7353 mL	1.4706 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.68 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Telaprevir (VX-950) is a highly selective, reversible, and potent peptidomimetic inhibitor of the HCV NS3-4A protease, the steady-state inhibitory constant (K_i) of Telaprevir is 7 nM against a genotype 1 (H strain) NS3 protease domain plus a NS4A cofactor peptide[1][2][3]. Telaprevir inhibits SARS-CoV-2 $3CL^{pro}$ activity[4].

IC_{50} & Target

Ki: 7 nM (genotype 1 HCV NS3-4A protease)[1]

In Vitro

Telaprevir (VX-950) is a covalent, reversible inhibitor of the NS3-4A protease with a slow-binding and slow-dissociation mechanism. Telaprevir exhibits significantly different kinetics in enzyme inhibition, which is most clearly exemplified by a very long half-life (58 min) of the bound enzyme-inhibitor complex. Telaprevir is additive to moderately synergistic with IFN-α in inhibiting HCV replication and in suppressing the emergence of resistance in replicon cells. Telaprevir reduces HCV RNA levels in a time- and dose-dependent manner. The IC_{50}s following a 24, 48, 72, and 120 h incubation with Telaprevir are

	determined to be 0.574, 0.488, 0.21, and 0.139 μM, respectively, indicating an increase in inhibitory effects with time. Following three independent experiments using the 48 h incubation in the presence of 2% FBS, the average IC_{50} of Telaprevir is determined to be 0.354 ± 0.035 μM, and the average IC_{90} is 0.830 ± 0.190 μM[1]. Telaprevir (VX-950) is a potent, selective, peptidomimetic inhibitor of the hepatitis C virus (HCV) NS3-4A serine protease, and Telaprevir demonstrates excellent antiviral activity both in genotype 1b HCV replicon cells (IC_{50}=354 nM) and in human fetal hepatocytes infected with genotype 1a HCV-positive patient sera (IC_{50}=280 nM)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	There is an ~5-fold reduction of serum SEAP activity in mice dosed with Telaprevir (VX-950) at either 10 or 25 mg/kg, which has an average value (±SEM) of 18.7±8.3% or 18.4±5.4%, respectively, compare to those administered vehicle (100±28%). These data demonstrates that Telaprevir is able to inhibit the HCV NS3-4A serine protease activity in mouse liver and block cleavage and subsequent secretion of SEAP into blood circulation in these mice[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Determination of IC_{50}, IC_{90}, CC_{50} of Telaprevir (VX-950) or IFN-α in HCV replicon cells is performed. Briefly, 1×10^4 replicon cells per well are plated in 96-well plates. On the following day, replicon cells is incubated at 37°C for the indicated period of time with antiviral agents serially diluted in DMEM plus 2% FBS and 0.5% DMSO. Total cellular RNA is extracted using an RNeasy-96 kit, and the copy number of HCV RNA is determined using a quantitative RT-PCR (QRT-PCR) assay. Each datum point represents the average of five replicates in cell culture. The cytotoxicity of Telaprevir is measured under the same experimental settings using a tetrazolium (MTS)-based cell viability assay. For the cytotoxicity assay with human hepatocyte cell lines, 1×10^4 parental Huh-7 cells per well or 4×10^4 HepG2 cells per well are used. To determine cytotoxicity of Telaprevir against resting PBMC, 1×10^5 cells per well are incubated with Telaprevir in RPMI-1640 medium (no serum) for 48 h, and the cell viability is determined by the MTS-based assay. To determine cytotoxicity of VX-950 against proliferating PBMC, 1×10^5 cells per well in RPMI-1640 medium are added to a 96-well plate, which is precoated with anti-human CD3 antibody. The cells are incubated with Telaprevir and anti-human CD28 antibody for 72 h at 37°C, and the cell growth is determined by [^{3}H]thymidine update between the 48th and 72nd h[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] Five groups of 6-week-old SCID mice (6 animals per group) are injected with 10^9 IFU per mouse of recombinant adenovirus Ad-WT-HCVpro-SEAP through the tail vein. Each group of mice is given two oral administrations of Telaprevir (VX-950) at one of the following doses: 10, 25, 75, 150, or 300 mg/kg. The first Telaprevir dose is given 2 h before the adenovirus injection, and the second dose is given 10 h after injection. An additional group of 10 mice is given vehicle alone. Serum samples are collected 24 h postinjection, and the SEAP activity in each Telaprevir-dosed group is compared to that of the vehicle group. Rat and Dog[2] The intravenous and oral pharmacokinetics of Telaprevir (VX-950) are evaluated in rats and dogs. A group of 3 male Sprague-Dawley rats weighing 250 to 300 g is administered an intravenous bolus dose of 0.95 mg/kg Telaprevir. Serial blood samples are collected in heparinized tubes before dosing and at 0.083, 0.167, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h after dose administration. A group of 3 male beagle dogs (8 to 12 kg) is administered an intravenous bolus dose of 3.5 mg/kg Telaprevir in 10% ethanol, 40% polyethylene glycol 400, and 50% D5W. Serial blood samples are collected in heparinized tubes before dosing and at 0.083, 0.167, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after dose administration. For oral studies in rats and dogs, Telaprevir is formulated in polyvinylpyrrolidone (PVP) K-30 plus 2% sodium lauryl sulfate and then dosed as an oral gavage. A group of 3 male Sprague-Dawley rats (250 to 300 g) is dosed orally with 40 mg/kg VX-950, and a group of 4 male beagle dogs (10.9 to 12.0 kg) is administered an oral dose of 9.6 mg/kg VX-950. In both oral studies, blood samples are taken before dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dose administration. In both intravenous and oral studies, plasma samples are obtained by centrifugation and stored at −70°C until analysis. Samples from the intravenous studies are analyzed by a chiral liquid chromatography followed by tandem mass spectrometry (LC/MS/MS) method, and samples from the oral studies are analyzed using an achiral LC/MS/MS method. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Signal Transduct Target Ther. 2021 May 29;6(1):212.
- ACS Cent Sci. February 2, 2022.
- Nat Commun. 2020 Sep 4;11(1):4417.
- Nat Commun. 2019 Aug 1;10(1):3468.
- Acta Pharm Sin B. 2019 Jul;9(4):769-781.

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REFERENCES

[1]. Lin K, et al. VX-950, a novel hepatitis C virus (HCV) NS3-4A protease inhibitor, exhibits potent antiviral activities in HCv replicon cells. Antimicrob Agents Chemother. 2006 May;50(5):1813-22.

[2]. Perni RB, et al. Preclinical profile of VX-950, a potent, selective, and orally bioavailable inhibitor of hepatitis C virus NS3-4A serine protease. Antimicrob Agents Chemother. 2006 Mar;50(3):899-909.

[3]. Zhang X, et al. Discovery and evolution of aloperine derivatives as a new family of HCV inhibitors with novel mechanism. Eur J Med Chem. 2018 Jan 1;143:1053-1065.

[4]. 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.

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