

## Product Data Sheet

Product Name: Telaprevir (VX-950)

Cat. No.: GC12299

### Chemical Properties

Cas. No. 402957-28-2

Chemical Name (3S,3aS,6aR)-2-[(2S)-2-[[[(2S)-2-cyclohexyl-2-(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carboxamide

SMILES CCCC(C(=O)C(=O)NC1CC1)NC(=O)C2C3CCCC3CN2C(=O)C(C(C)(C)C)NC(=O)C(C4CCCC4)NC(=O)C5=NC=CN=C5

Formula C<sub>36</sub>H<sub>53</sub>N<sub>7</sub>O<sub>6</sub>

M.Wt 679.9

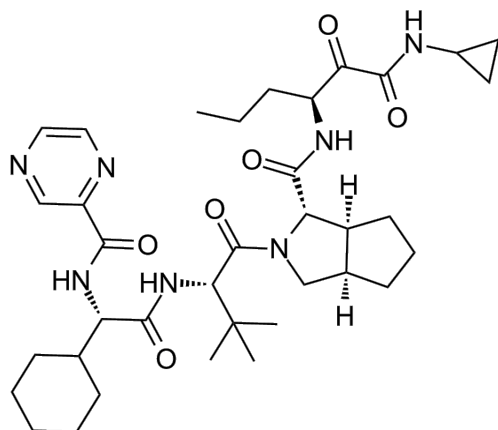
Solubility ≥ 32.95 mg/mL in DMSO

Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



### Protocol

Cell experiment [1]:

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Cell lines                      Con1 (genotype 1b) subgenomic HCV replicon cells, Primary human fetal liver cells

Preparation method        The solubility of this compound in DMSO is >33 mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reacting condition        5 or 50 µM, 48 h

Applications                VX-950 reduced HCV RNA levels in a time- and dose-dependent manner. The IC<sub>50</sub>s following a 24-, 48-, 72-, and 120-h incubation with VX-950 were 0.574, 0.488, 0.210, and 0.139 µM, respectively. VX-950 (30 µM) showed no significant cytotoxicity in both parental Huh-7 and HepG2 cell lines. VX-950 reduced HCV proteins in the replicon cells. VX-950 showed no cytotoxicity in proliferating PBMC. VX-950 induced a multilog reduction of HCV RNA levels in replicon cells. VX-950 inhibited HCV replication in primary human fetal liver cells.

### Animal experiment [2]:

Animal models              HCV NS3-4A protease mouse model

Dosage form                Oral administration, 10-300 mg/kg

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**Application**

Oral administration of VX-950 in a PVP polymer matrix resulted in good exposure in rats and dogs. VX-950 inhibited HCV NS3-4A serine protease and reduced SEAP levels in the NS3-4A protease mouse model. Oral administration of VX-950 reduced HCV protease-dependent cleavage and subsequent secretion of SEAP from the liver into the blood in the mice model to 18.7% and 18.4% at dosage of 10 and 25 mg/kg, respectively.

**Other notes**

Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

### References:

[1]. Lin K, Perni R B, Kwong A D, et al. VX-950, a novel hepatitis C virus (HCV) NS3-4A protease inhibitor, exhibits potent antiviral activities in HCV replicon cells[J]. Antimicrobial agents and chemotherapy, 2006, 50(5): 1813-1822.

[2]. Perni R B, Almquist S J, Byrn R A, et al. Preclinical profile of VX-950, a potent, selective, and orally bioavailable inhibitor of hepatitis C virus NS3-4A serine protease[J]. Antimicrobial agents and chemotherapy, 2006, 50(3): 899-909.

### Background

Telaprevir 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.

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- $\alpha$  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

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Telaprevir are determined to be 0.574, 0.488, 0.21, and 0.139  $\mu\text{M}$ , 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  $\text{IC}_{50}$  of Telaprevir is determined to be  $0.354 \pm 0.035 \mu\text{M}$ , and the average  $\text{IC}_{90}$  is  $0.830 \pm 0.190 \mu\text{M}$ [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 ( $\text{IC}_{50}$ =354 nM) and in human fetal hepatocytes infected with genotype 1a HCV-positive patient sera ( $\text{IC}_{50}$ =280 nM)[2].

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 ( $\pm\text{SEM}$ ) of  $18.7 \pm 8.3\%$  or  $18.4 \pm 5.4\%$ , respectively, compare to those administered vehicle ( $100 \pm 28\%$ ). 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].

### 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.

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