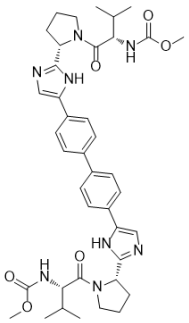
Daclatasvir



Cat. No.:	HY-10466		
CAS No.:	1009119-64-5		
Molecular Formula:	$C_{40}H_{50}N_8O_6$		
Molecular Weight:	738.88		
Target:	HCV Protease; HCV		
Pathway:	Metabolic Enzyme/Protease; Anti-infection		
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 : ≥ 40 mg/mL (54.14 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.3534 mL	6.7670 mL	13.5340 mL
	5 mM	0.2707 mL	1.3534 mL	2.7068 mL
	10 mM	0.1353 mL	0.6767 mL	1.3534 mL

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

In Vivo

1. Daclatasvir is prepared in vehicle (ddH_2O)[3].

BIOLOGICAL ACTIVITY

Description

Daclatasvir is a potent **HCV NS5A** protein inhibitor, with mean **EC_{50}** values of 50 and 9 pM against genotype 1a and 1b replicons, respectively.

IC_{50} & Target

EC50: 9±4 pM (HCV replicon genotype 1b, in Con1 cells), 50 ± 13 pM (HCV replicon genotype 1a, in H77 cells)[1]

In Vitro

Daclatasvir (BMS-790052) is a small molecule inhibitor of the HCV NS5A protein that exhibits picomolar half-maximum effective concentrations (EC_{50}) towards replicons expressing a broad range of HCV genotypes and the JFH-1 genotype 2a infectious virus in cell culture. Daclatasvir is a potent inhibitor of the JFH-1 genotype 2a infectious virus that replicates in cell culture (EC_{50}=28 pM), an assay considered to be a more biologically relevant in vitro cell culture system. In addition, Daclatasvir displays similar potency in Huh-7, HeLa and HEK293T cells, demonstrating that the function(s) of NS5A inhibited by Daclatasvir is (are) highly conserved in different cellular environments[1].

In Vivo	In a randomized, double-blind, placebo-controlled, single ascending-dose study, Daclatasvir (BMS-790052) is administered at six dose levels to healthy, non-HCV-infected subjects over a range of 1 to 200 mg as an oral solution. Daclatasvir is safe and well tolerated up to 200 mg with no clinically relevant adverse effects. After oral administration, Daclatasvir is readily absorbed, with dose-proportional exposures over the studied dose range, and all subjects have drug concentrations greater than the protein-binding-adjusted EC_{90} for genotypes 1a and 1b, as measured in the replicon assay, at and beyond 24 h post-dose. (The protein binding-adjusted EC_{90} figures are derived from an analysis of the effect of the addition of human serum on antiviral activity in replicons. In the presence of 40% human serum, the EC_{90} for Daclatasvir is 383 pM (0.28 ng/mL) for the genotype 1a replicon and 49 pM (0.04 ng/mL) for the genotyope 1b replicon)[1]. Mice in each group that developed persistent HCV infection are divided into two treatment groups. One group receive 4 weeks of Asunaprevir/Daclatasvir treatment and the other group received 4 weeks of Ledipasvir/GS-558093 treatment. Asunaprevir/Daclatasvir therapy and Ledipasvir/GS-558093 therapy rapidly decease serum HCV RNA levels to below the sensitivity, and they are not detected after completion of the therapy except for two mice in the Ledipasvir/GS-558093 group[2].

PROTOCOL

Cell Assay [1]	HCV genotype 1a and 1b replicon cells are maintained in media containing Daclatasvir at a concentration of 5- to 20-fold above EC_{50} and 0.5 mg/mL G418. Replicon cells similarly treated with DMSO are maintained as controls. After approximately 4-5 weeks when cell growth is similar to DMSO-treated control cells, selected cells are expanded for resistance testing and analysis by PCR with reverse transcription[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] Humanized liver chimeric mice, whose chimeric rate of the liver is estimated as over 40 %, are injected intravenously with 100 μL of HCV-positive human serum samples. After inoculation, their blood is collected from an external jugular vein every 1-4 weeks. The HCV RNA levels are measured by the COBAS TaqMan HCV test in 100-fold diluted serum with a lower measurement range of 3.2 log IU/mL serum. After serum levels of HCV RNA reach plateau levels, mice are administered orally once a day for 4 weeks with one of the following: 40 mg/kg of Asunaprevir plus 30 mg/kg of Daclatasvir, 15 mg/kg of Ledipasvir plus 50 mg/kg of GS-558093 and 50 mg/kg of GS-558093 plus 400 mg/kg of Telaprevir. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- **Hepatology**. 2019 May;69(5):1861-1872.
- **EMBO Rep**. 2016 Jul;17(7):1013-28.
- **PLoS Pathog**. 2018 Sep 18;14(9):e1007284.
- **PLoS Pathog**. 2017 May 11;13(5):e1006374.
- **J Gastroenterol**. 2019 Jan 25.

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REFERENCES

[1]. Gao M, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. Nature. 2010 May 6;465(7294):96-100.

[2]. Kai Y, et al. Emergence of hepatitis C virus NS5A L31V plus Y93H variant upon treatment failure of daclatasvir and asunaprevir is relatively resistant to ledipasvir and NS5B polymerase nucleotide inhibitor GS-558093 in human hepatocyte chimeric mice. J Ga

[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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