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产品名称：Daclatasvir (BMS-790052)
产品别名：Daclatasvir；达卡他韦

生物活性：

Description	Daclatasvir is a potent HCV NS5A protein inhibitor, with mean EC50 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 (EC50) 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 (EC50=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 EC90 for genotypes 1a and 1b, as measured in the replicon assay, at and beyond 24 h post-dose. (The protein binding-adjusted EC90 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 EC90 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].

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

*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。

Solvent&Solubility	***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： ——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 (3.38 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.38 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% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (3.38 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.38 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 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (3.38 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.38 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]. 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.

实验参考：

Cell Assay	HCV genotype 1a and 1b replicon cells are maintained in media containing Daclatasvir at a concentration of 5- to 20-fold above EC50 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].
	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

Animal Administration	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.
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.