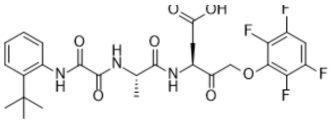
Emricasan

Cat. No.:	HY-10396
CAS No.:	254750-02-2
Molecular Formula:	$C_{26}H_{27}F_4N_3O_7$
Molecular Weight:	569.5
Target:	Caspase; Flaviviridae
Pathway:	Apoptosis; 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 : 100 mg/mL (175.59 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7559 mL	8.7796 mL	17.5593 mL
	5 mM	0.3512 mL	1.7559 mL	3.5119 mL
	10 mM	0.1756 mL	0.8780 mL	1.7559 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.5 mg/mL (4.39 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (4.39 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.39 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Emricasan (PF 03491390) is an orally active and irreversible pan-caspase inhibitor. Emricasan inhibits Zika virus (ZIKV)-induced increases in caspase-3 activity and protected human cortical neural progenitors[1].

IC_{50} & Target

Caspase

In Vitro

Emricasan (PF 03491390; IDN-6556) (50 μM; 24 hours) directly improves hepatocytes phenotype in primary rat cirrhotic hepatocytes[1].

	Emricasan (10-50 μM) has hepatoprotective effects in human liver cells[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Emricasan (PF 03491390; IDN-6556) is orally active that is retained in the liver for a prolonged period of time. TUNEL-positive cells are considerably increased by five-fold in mice fed a HFD and are reduced under Emricasan treatment. In accordance with this observation caspase-3 and -8 are increased in HFD-fed mice by 1.5- and 1.3-fold respectively and are significantly decreased by Emricasan treatment[2]. When comparing efficacy by multiple routes of administration, Emricasan is administered i.p., p.o., i.m., or i.v. (0.03-3 mg/kg). Caspase 3-like activities, measured as DEVD-AMC cleavage, dose dependently decreased with a 92.5% reduction after the highest dose of Emricasan (3 mg/kg). Emricasan is initially tested in the α-Fas model of liver injury, marked hepatocellular apoptosis, and peak ALT activities within 6 h. Emricasan is administered i.p. immediately after administration of α-Fas, ALT activities, measured 6 h later, decreased in a dose-dependent manner with an ED50 value of 0.08 (0.06-0.12) mg/kg[3]. Emricasan is a highly selective pan-caspase inhibitor demonstrating irreversible inhibition and a significant first-pass effect. In both syngeneic mouse islets and human islets transplanted into immunodeficient mice, Emricasan (i.p., 20 mg/kg) given for 7 days post-transplant led to a significantly enhanced rate of diabetes reversal as compared to vehicle[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [2][3]	Mice[2] The male C57BL/6J mice are age-matched and used at approximately 12-16 weeks of age. Four groups are studied (n=60) with 15 mice per group. Groups 1 and 3 receive regular chow. Groups 2 and 4 receive HFD and 50 g/L (Sucrose) is added to drinking water for 20 weeks. Groups 3 and 4 receive Emricasan 0.3 mg/kg/day per os, and Group 1 and 2 receive the vehicle. The oral administration of Emricasan at doses of 0.3 mg/kg corresponds to the ED90 value to prevent liver injury in the model of α-Fas-induced liver injury. Total body weight is measured at 0, 5, 10, 15 and 20 weeks. Rats[3] The male Sprague-Dawley rats are used. Blood (100 μL/sample) is taken from the carotid cannula 2 to 240 min after administration of Emricasan (i.v., s.c., p.o., or i.p.). Serum is prepared and frozen immediately until analysis. In studies measuring drug concentrations in portal and systemic blood, individual rats are bled (three animals per time point) simultaneously from the portal vein and inferior vena cava. In the biliary excretion study, bile is collected from the common bile duct after i.v. and p.o. administration of Emricasan (10 mg/kg) over a 24-h period on ice and frozen until analysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2019 Nov;575(7784):683-687.
- J Exp Med. 2018 Jul 2;215(7):1839-1852.
- Nat Protoc. 2015 May;10(5):807-21.
- Acta Pharm Sin B. 2019 May;9(3):526-536.
- Cell Death Differ. 2022 Jan 22.

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REFERENCES

[1]. Barreyro FJ, et al. The pan-caspase inhibitor Emricasan (IDN-6556) decreases liver injury and fibrosis in a murine model of non-alcoholic steatohepatitis. Liver Int. 2015

Mar;35(3):953-66.

[2]. Hoglen NC, et al. Characterization of IDN-6556 (3-[2-(2-tert-butyl-phenylaminooxalyl)-amino]-propionylamino]-4-oxo-5-(2,3,5,6-te trafluoro-phenoxy)-pentanoic acid): a liver-targeted caspase inhibitor. J Pharmacol Exp Ther. 2004 May;309(2):634-40.

[3]. McCall M, et al. The caspase inhibitor IDN-6556 (PF3491390) improves marginal mass engraftment after islet transplantation in mice. Surgery. 2011 Jul;150(1):48-55.

[4]. Tian J, et al. Combination of Emricasan with AP24534 Synergistically Reduces Ischemia/Reperfusion Injury in Rat Brain Through Simultaneous Prevention of Apoptosis and Necroptosis. Transl Stroke Res. 2017 Nov 4.

[5]. Gracia-Sancho J, et al. Emricasan Ameliorates Portal Hypertension and Liver Fibrosis in Cirrhotic Rats Through a Hepatocyte-Mediated Paracrine Mechanism. Hepatol Commun. 2019 Apr 22;3(7):987-1000.

[6]. Xu M, et al. Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. Nat Med. 2016 Oct;22(10):1101-1107.

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