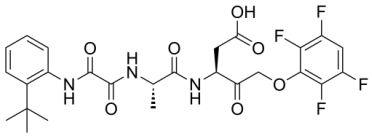
Data Sheet

Product Name:	Emricasan
Cat. No.:	CS-0599
CAS No.:	254750-02-2
Molecular Formula:	$C_{26}H_{27}F_4N_3O_7$
Molecular Weight:	569.50
Target:	Caspase; Flavivirus
Pathway:	Anti-infection; Apoptosis
Solubility:	DMSO : 100 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

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]. IC50 & Target:pan-caspase[1] ***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].

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].

PROTOCOL (Extracted from published papers and Only for reference)

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.

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.

CAIndexNames:

L-Alaninamide, N-[2-(1,1-dimethylethyl)phenyl]-2-oxoglycyl-N-[(1S)-1-(carboxymethyl)-2-oxo-3-(2,3,5,6-tetrafluorophenoxy)propyl]-

SMILES:

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Caution: Product has not been fully validated for medical applications. For research use only.

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