

Product Data Sheet

Product Name: Vorapaxar

Cat. No.: GC17545

Chemical Properties

Cas. No. 618385-01-6

Chemical Name ethyl N-[(1R,3aR,4aR,6R,8aR,9S,9aS)-9-[(E)-2-[5-(3-fluorophenyl)pyridin-2-yl]ethenyl]-1-methyl-3-oxo-3a,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-benzo[f][2]benzofuran-6-yl]carbamate

SMILES CCOC(=O)NC1CCC2C(C1)CC3C(C2C=CC4=NC=C(C=C4)C5=CC(=CC=C5)F)C(OC3=O)C

Formula $C_{29}H_{33}FN_2O_4$

M.Wt 492.58

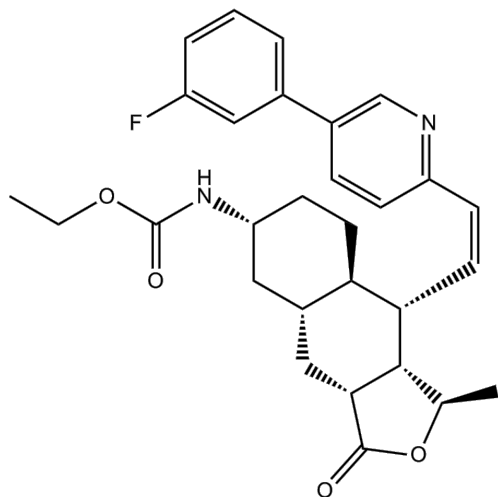
Solubility $\geq 24.65\text{mg/mL}$ in DMSO

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 mouse lung fibroblasts (MLG cells) and human lung fibroblasts (HFL1 cells)

Preparation Method MLG or HFL1 cells were inoculated in a 12-well plate. After washing with phosphate buffer, MLG or HFL1 cells were cultured with Vorapaxar (0.2, 0.5 and 1 μ M) and thrombin (1U/ml).

Reaction Conditions 0.2, 0.5 and 1 μ M; 24h

Applications Vorapaxar can effectively inhibit thrombin-activated pulmonary fibrosis by inhibiting the interaction between HSP90 β and TGF- β receptor II, inhibiting TGF- β activation of its receptor, and thus inhibiting TGF- β -mediated Smad2/3 phosphorylation.

Animal experiment [2]:

Animal models C57BL/6 mice

Preparation Method Hepatic partial-warm ischemia-reperfusion injury (IRI) models were established in mice. All mice were randomly allocated to two IRI groups. The IRI + Vorapaxar group received intraperitoneal administration of 5mg/kg of Vorapaxar, whereas the IRI + vehicle group received intraperitoneal administration of vehicle (1% DMSO equivalent to that used to dissolve Vorapaxar) at 60min before ischemia and immediately after reperfusion.

Dosage form 5mg/kg; i.p.; before ischemia and immediately after reperfusion

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Applications In IRI mice models, Vorapaxar treatment significantly decreased serum transaminase levels, improved liver histological damage, reduced the number of apoptotic cells, and induced extracellular signal-regulated kinase 1/2 (ERK 1/2) cell survival signaling.

References:

- [1] Xiao T, Ren S F, Bao J L, et al. Vorapaxar proven to be a promising candidate for pulmonary fibrosis by intervening in the PAR1/JAK2/STAT1/3 signaling pathway-an experimental in vitro and vivo study. Eur J Pharmacol. 2023 Mar 15;943:175438.
- [2] Noguchi D, Kuriyama N, Ito T, et al. Antiapoptotic Effect by PAR-1 Antagonist Protects Mouse Liver Against Ischemia-Reperfusion Injury. J Surg Res. 2020 Feb;246:568-583.

Background

Vorapaxar is an orally active, selective, and competitive antagonist of the thrombin receptor protease-activated receptor (PAR-1), with a K_D value of 1.27 ± 0.3 nM. Its K_i value increases as plasma concentration rises, reaching 39.2 nM at 100% plasma.^[1] Vorapaxar has shown anti-fibrotic and anti-cancer potential^{[2][3]}. The anti-platelet properties of Vorapaxar further contribute to its efficacy in preventing thrombosis and improving outcomes in patients with cardiovascular conditions^{[1][4][5]}.

In vitro, Vorapaxar treatment (0.2, 0.5 and 1 μ M) on mouse lung fibroblasts (MLG cells) and human lung fibroblasts (HFL1 cells) for 24h inhibited the migration of thrombin-activated fibroblasts and reduced the expression of fibroblast activation markers α -SMA, collagen I and fibronectin proteins in a dose-dependent manner by weakening the binding of HSP90 β and TGF beta receptor type II and inhibiting TGF- β -mediated Smad2/3 phosphorylation^[2]. Preincubation of three epithelial ovarian cancer cell lines (SKOV-3, OVCAR-3 and CaOV-3) with Vorapaxar (5nM) for 1h reduced thrombin induced cellular proliferation back to basal levels. These results provides a basis for the potential application of Vorapaxar in the treatment of ovarian cancer^[3].

In vivo, Vorapaxar (30 μ g/kg) was administrated into Doxorubicin-induced cardiac injury mice model via oral gavage daily for 5 days. The results showed that Vorapaxar improved the heart function of WT mice to levels seen in PAR-1^{-/-} mice after Doxorubicin injection. This suggests that Vorapaxar

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could reduce the cardiotoxic effects of Doxorubicin in patients^[5]. The hepatic ischemia-reperfusion injury (IRI) mice model received intraperitoneal administration of 5mg/kg of Vorapaxar. Vorapaxar treatment exerted antiapoptotic effect and ameliorated hepatocellular injury by attenuating activation of caspase9 and markedly inducing phosphorylation of both AKT and ERK 1/2^[6]. Vorapaxar (1.75mg/kg) administered orally twice a week into streptozotocin-induced diabetic mice model for 20 weeks prevented mice developing significant albuminuria, mesangial expansion and glomerular fibronectin deposition. The results showed that PAR-1 inhibition by Vorapaxar prevented the development of diabetic nephropathy^[7].

References:

- [1] Hawes B E, Zhai Y, Hesk D, et al. In vitro pharmacological characterization of vorapaxar, a novel platelet thrombin receptor antagonist. *Eur J Pharmacol.* 2015 Sep 5;762:221-8.
- [2] Xiao T, Ren S F, Bao J L, et al. Vorapaxar proven to be a promising candidate for pulmonary fibrosis by intervening in the PAR1/JAK2/STAT1/3 signaling pathway-an experimental in vitro and vivo study. *Eur J Pharmacol.* 2023 Mar 15;943:175438.
- [3] Chanakira A, Westmark P R, Ong I M, Sheehan J P. Tissue factor-factor VIIa complex triggers protease activated receptor 2-dependent growth factor release and migration in ovarian cancer. *Gynecol Oncol.* 2017 Apr;145(1):167-175.
- [4] Leonardi S, Tricoci P, Becker R C. Protease-activated receptor-1 inhibitors: a novel class of antiplatelet agents for the treatment of patients with acute coronary syndrome. *Adv Cardiol.* 2012;47:87-99.
- [5] Antoniak S, Tatsumi K, Schmedes C M, et al. Protease-activated receptor 1 activation enhances doxorubicin-induced cardiotoxicity. *J Mol Cell Cardiol.* 2018 Sep;122:80-87.
- [6] Noguchi D, Kuriyama N, Ito T, et al. Antiapoptotic Effect by PAR-1 Antagonist Protects Mouse Liver Against Ischemia-Reperfusion Injury. *J Surg Res.* 2020 Feb;246:568-583.
- [7] Waasdorp M, Duitman J, Florquin S, Spek C A. Vorapaxar treatment reduces mesangial expansion in streptozotocin-induced diabetic nephropathy in mice. *Oncotarget.* 2018 Apr 24;9(31):21655-21662.

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