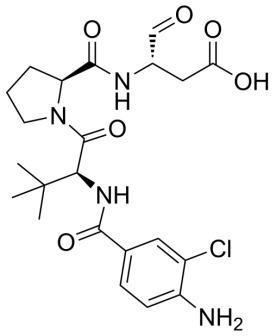
VRT-043198

Cat. No.:	HY-112226
CAS No.:	244133-31-1
Molecular Formula:	$C_{22}H_{29}ClN_4O_6$
Molecular Weight:	480.94
Target:	Caspase; Drug Metabolite
Pathway:	Apoptosis; Metabolic Enzyme/Protease
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 : 180 mg/mL (374.27 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0793 mL	10.3963 mL	20.7926 mL
	5 mM	0.4159 mL	2.0793 mL	4.1585 mL
	10 mM	0.2079 mL	1.0396 mL	2.0793 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: 4.5 mg/mL (9.36 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 4.5 mg/mL (9.36 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 4.5 mg/mL (9.36 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

VRT-043198, the agent metabolite of VX-765 (Belnacasan), is a potent, selective and blood-brain barrier permeable inhibitor of interleukin-converting enzyme/caspase-1 subfamily caspases. VRT-043198 exhibits K_i values of 0.8 nM and 0.6 nM for ICE/caspase-1 and caspase-4, respectively[1].

IC_{50} & Target		
	Caspase-1 0.8 nM (Ki)	Caspase-4 0.6 nM (Ki)

In Vitro	VRT-043198 exhibits 100- to 10,000-fold selectivity against other caspase-3 and -6 to -9[1]. VRT043198 inhibits the release of interleukin (IL)-1β and IL-18, but it has little effect on the release of several other cytokines, including IL-1α, tumor necrosis factor-, IL-6 and IL-8. VRT-043198 inhibited IL-1β release from both PBMCs (n = 8) and whole blood (n = 4) with IC_{50} values of 0.67±0.55 and 1.9±0.80 nM, respectively[1]. VRT-043198 lacks potent antiapoptotic activity[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	VX-765 is converted rapidly to VRT-043198 under the action of plasma and liver esterases and also much more slowly in aqueous solution[1]. VX765 reduces disease severity and the expression of inflammatory mediators in models of rheumatoid arthritis and skin inflammation[1]. VX765 (25, 50, 100, or 200 mg/kg) inhibits lipopolysaccharide-induced cytokine secretion[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Naïve male CD-1 mice[1].
Dosage:	25-200 mg/kg.
Administration:	Oral gavage 1 h before i.v. injection of 2 mg/kg E. coli LPS (strain 0111:B4).
Result:	Reduced serum IL-1β levels.

CUSTOMER VALIDATION

- Neuropsychiatr Dis Treat. 2022 May 16;18:1027-1037.

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REFERENCES

[1]. Woods Wannamaker, et al. (S)-1-((S)-2-{[1-(4-amino-3-chloro-phenyl)-methanoyl]-amino}-3,3-dimethyl-butanoyl)-pyrrolidine-2-carboxylic acid ((2R,3S)-2-ethoxy-5-oxo-tetrahydro-furan-3-yl)-amide (VX-765), an orally available selective interleukin (IL)-converting enzyme/caspase-1 inhibitor, exhibits potent anti-inflammatory activities by inhibiting the release of IL-1beta and IL-18. J Pharmacol Exp Ther. 2007 May;321(2):509-16.

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