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Caspase-1/4 Inhibitor, VX-765 - CAS 273404-37-8 - Calbiochem A cell-permeable prodrug that upon conversion to its active form inhibits caspase-1 and 4 activity (Ki = 800 pM and 600 pM, respectively).

Art. ID SAF-5313720001

Unit EA

Description

An enhanced cell-permeable, non-toxic, orally available masked aspartaldehyde prodrug that is converted to its active metabolite, VRT-043198, both in vitro and in vivo via hydrolytic cleavage by esterases. The active metabolite displays anti- inflammatory and anticonvulsant properties. Binds to the active site of caspase-1 and caspase-4 with high affinity to inhibit their activity (Ki = 800 pM and 600 pM, respectively). Does not affect the activities of trypsin, cathepsin B and has much reduced effect on other caspases (Ki = 100 nM to 21.5 &#181,M) and granzyme B (Ki = 900 nM). Recently shown to inhibit pyroptosis and prevent CD4 T-cell death by HIV-1. Also shown to block the release of lipopolysaccharide- induced IL-1beta and IL-18 in human PBMC (IC50 = 700 pM). Blocks Staphalococcus aureus - Cowen strain I-stimulated production of IL-1beta, IL-18, and IFN-gamma in human PBMCs (IC50 = 870 nM and 2.8 and 5.6 &#181,M, respectively), but does not affect the TNF-alpha levels (IC50 >50 &#181,M). Appears to cross the blood brain barrier to block seizure-induced IL-1beta production and delay the onset and reduces the duration of seizures in rats (50 mg/kg, i.p.).Please note that the molecular weight for this compound is batch-specific due to variable water content., The cell-permeable prodrug of the caspase-1/4-selective inhibitor VRT-43198 (Ki in nM = <0.6/Caspase-4, 0.8/Caspase-1, 100/Caspase-8, 560/Caspase-6, 1,030/Caspase-9, 9,000/Granzyme B, 16,000/Caspase-7, 21,500/Caspase-3, IC50 >100 &#181,M against Cathepsin B & Trypsin). In addition to inhibiting LPS-induced IL-1beta production in primary human PBMC cultures (IC50 ~1 &#181,M), VX-765 is also effective in preventing HIV infection-induced IL-1beta production and pyroptosis of CD4 T cells in human lymphoid aggregate cultures (HLAC, CD4 population = 29.2% in non-infected control cultures, 8.3% vs. 30.2% in infected cultures with or without 5 &#181,M VX-765). VX-765 is orally available in mice (Blood Cmax = 0.78 &#181,g/mL = 1.53 &#181,M, Tmax = 1.0 h, AUClast = 2.06 &#181,g . h/mL, 84 mg/kg, p.o.) and shown to display in vivo anti-inflammatory efficacy against LPS-induced plasma IL-1beta production (EDmax = 100 mg/kg, p.o.), Oxazolone-induced delayed-type hypersensitivity (EDmax = 50 mg/kg, p.o.), collagen-induced arthritis (EDmax = 100 mg/kg, p.o.). When administered via intraperitoneal injection, VX-765 is also demonstrated to suppress the severity of seizure induction (EDmax = 50 mg/kg i.p.) among rats receiving kainic acid via intracerebroventricular injection.

Text/Information	Analyte/Parameter	CAS number	Concentration/Value	Unit	Method	Source
	VX-765	[273404-37-8]				