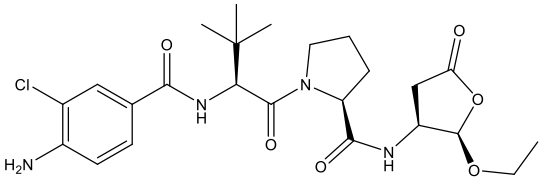
Catalog # 10-4399
Belnacasan

CAS# 273404-37-8

(S)-1-((S)-2-(4-Amino-3-chlorobenzamido)-3,3-dimethylbutanoyl)-N-((2R,3S)-2-ethoxy-5-oxotetrahydrofuran-3-yl)pyrrolidine-2-carboxamide; VX-765

Lot # FBS2105



Belnacasan is a prodrug of VRT-043198, a potent (Ki = 0.8 nM ICE/caspase-1; <0.6nM caspase-4) and selective inhibitor of interleukin-converting enzyme/caspase-1 subfamily caspases.[1] VRT-043198 ICE/caspase-1 IC_{50} = 0.67 µM PBMCs, 1.0 µM whole blood. It inhibited the release of IL-1β and IL-18 from human monocytes in vitro and their production in vivo in models of inflammation. Belnacasan inhibited the activation and expression of the NLRP3 Inflammasome leading to moderation of depressive-like behaviors induced by chronic mild stress[2] and prevention of glial pyroptosis in multiple sclerosis models[3]. It inhibited pyroptosis in vascular smooth muscle cells during atherogenesis suggesting a possible therapeutic effect in treating atherosclerotic disease.[4] Belnacasan reduced acute seizures and drug resistant chronic epileptic activity in mice[5] and provided neuroprotection in two rat models of temporal lobe epilepsy[6]. It also displays protective effects in models of stroke[7]and Alzheimer's disease[8].

1) Wannamaker *et al.* (2007) *(S)-1-((S)-2-{[1-(4-Amino-3-chlorophenyl)-methanoyl]-amino}-3,3-dimethylbutanoyl)-pyrrolidine-2-carboxylic acid ((2R,3S)-2-ethoxy-5-oxotetrahydrofuran-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-1β and IL-18,* J. Pharmacol. Exp. Ther. **321** 509
2) Zhang *et al.* (2015) *NLRP3 Inflammasome Mediates Chronic Mild Stress-Induced Depression in Mice via Neuroinflammation,* Int. J. Neuropsychopharmacol. **18** pyv006
3) McKenzie *et al*. (2018) *Caspase-1 inhibition prevents glial inflammasome activation and pyroptosis in models of multiple sclerosis,* Proc. Natl. Acad. Sci USA **115** E6065
4) Li *et al*. (2020) *VX-765 attenuates atherosclerosis in ApoE deficient mice by modulating VSMCs pyroptosis,* Exp. Cell Res. **389** 111847
5) Maroso *et al.* (2011) *Interleukin-1b biosynthesis inhibition reduces acute seizures and drug resistant chronic epileptic activity in mice*, Neurotherapeutics **8** 304
6) Noe *et al.* (2013) *Pharmacological blockade of IL-1b/IL-1 receptor type 1 axis during epileptogenesis provides neuroprotection in two rat models of temporal lobe epilepsy,* Neurobiol. Dis. **59** 183
7) Li *et al.* (2019) *Caspase-1 inhibition mediates neuroprotection in experimental stroke by polarizing M2 microglia/macrophage and suppressing NF-kB activation,* Biochem. Biophys. Res. Commun. **513** 479
8) Flores *et al.* (2018) *Caspase-1 inhibition alleviates cognitive impairment in an Alzheimer's disease mouse model,* Nat. Commun. **9** 3916

PHYSICAL DATA

Molecular Weight:	508.99
Molecular Formula:	$C_{24}H_{33}ClN_4O_6$
Purity:	>98% (HPLC)
Solubility:	DMSO (>25 mg/mL)
Physical Description:	Off-white to white solid
Storage and Stability:	Store as supplied at -20°C for up to one year from the date of purchase. Solutions in DMSO may be stored at -20°C for up to 2 months

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