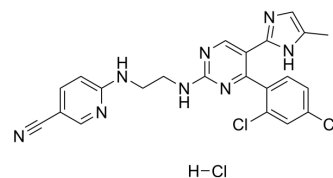


Laduviglusib monohydrochloride

Cat. No.:	HY-10182A
CAS No.:	1797989-42-4
Molecular Formula:	C ₂₂ H ₁₉ Cl ₃ N ₈
Molecular Weight:	501.8
Target:	GSK-3; Autophagy; Wnt; β-catenin
Pathway:	PI3K/Akt/mTOR; Stem Cell/Wnt; Autophagy
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 60 mg/mL (119.57 mM; Need ultrasonic)
H₂O : 7.14 mg/mL (14.23 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent Concentration	Mass		
		1 mg	5 mg	10 mg
	1 mM	1.9928 mL	9.9641 mL	19.9283 mL
	5 mM	0.3986 mL	1.9928 mL	3.9857 mL
	10 mM	0.1993 mL	0.9964 mL	1.9928 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

- Add each solvent one by one: PBS
Solubility: 5 mg/mL (9.96 mM); Clear solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
Solubility: ≥ 3 mg/mL (5.98 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: ≥ 3 mg/mL (5.98 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 3 mg/mL (5.98 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Laduviglusib (CHIR-99021) monohydrochloride is a potent and selective GSK-3α/β inhibitor with IC₅₀s of 10 nM and 6.7 nM. Laduviglusib monohydrochloride shows >500-fold selectivity for GSK-3 over CDC2, ERK2 and other protein kinases. Laduviglusib monohydrochloride is also a potent Wnt/β-catenin signaling pathway activator. Laduviglusib monohydrochloride enhances mouse and human embryonic stem cells self-renewal. Laduviglusib monohydrochloride induces autophagy^{[1][2][3]}.

IC₅₀ & Target	GSK-3β 6.7 nM (IC ₅₀)	GSK-3α 10 nM (IC ₅₀)	cdc2 8800 nM (IC ₅₀)
In Vitro	Laduviglusib monohydrochloride inhibits human GSK-3β with K _i values of 9.8 nM ^[1] . Laduviglusib monohydrochloride is a small organic molecule that inhibits GSK3α and GSK3β by competing for their ATP-binding sites. In vitro kinase assays reveal that Laduviglusib monohydrochloride specifically inhibits GSK3β (IC ₅₀ ~5 nM) and GSK3α (IC ₅₀ ~10 nM), with little effect on other kinases ^[4] . In the presence of Laduviglusib monohydrochloride the viability of the ES-D3 cells is reduced by 24.7% at 2.5 μM, 56.3% at 5 μM, 61.9% at 7.5 μM and 69.2% at 10 μM Laduviglusib monohydrochloride with an IC ₅₀ of 4.9 μM ^[2] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.		
In Vivo	In ZDF rats, a single oral dose of Laduviglusib (16 mg/kg or 48 mg/kg) monohydrochloride rapidly lowers plasma glucose, with a maximal reduction of nearly 150 mg/dl 3-4 h after administration ^[1] . Laduviglusib (2 mg/kg) monohydrochloride given once, 4 h before irradiation, significantly improves survival after 14.5 Gy abdominal irradiation (ABI). Laduviglusib monohydrochloride treatment significantly blocks crypt apoptosis and accumulation of p-H2AX ⁺ cells, and improves crypt regeneration and villus height. Laduviglusib monohydrochloride treatment increases Lgr5 ⁺ cell survival by blocking apoptosis, and effectively prevents the reduction of Olfm4, Lgr5 and CD44 as early as 4 h ^[5] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.		

PROTOCOL

Cell Assay ^[3]	The viability of the mouse ES cells is determined after exposure to different concentrations of GSK3 inhibitors for three days using the MTT assay. The decrease of MTT activity is a reliable metabolism-based test for quantifying cell viability; this decrease correlates with the loss of cell viability. 2,000 cells are seeded overnight on gelatine-coated 96-well plates in LIF-containing ES cell medium. On the next day the medium is changed to medium devoid of LIF and with reduced serum and supplemented with 0.1-1 μM BIO, or 1-10 μM SB-216763, CHIR-99021 or CHIR-98014. Basal medium without GSK3 inhibitors or DMSO is used as control. All tested conditions are analyzed in triplicates ^[3] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration ^{[1][4]}	<p>Rats^[1]</p> <p>Primary hepatocytes from male Sprague Dawley rats that weighed <140 g are prepared and used 1-3 h after isolation. Aliquots of 1×10⁶ cells in 1 mL of DMEM/F12 medium plus 0.2% BSA and CHIR-99021 (orally at 16 or 48 mg/kg) or controls are incubated in 12-well plates on a low-speed shaker for 30 min at 37°C in a CO₂-enriched atmosphere, collected by centrifugation and lysed by freeze/thaw in buffer A plus 0.01% NP40; the GS assay is again performed.</p> <p>Mice^[4]</p> <p>Mice 6-10 weeks old are used. The PUMA^{+/+} and PUMA^{-/-} littermates on C57BL/6 background (F10) and Lgr5-EGFP (Lgr5-EGFP-IRES-creERT2) mice are subjected to whole body irradiation (TBI), or abdominal irradiation (ABI). Mice are injected intraperitoneally (i.p.) with 2 mg/kg of CHIR99021 4 h before radiation or 1 mg/kg of SB415286 28 h and 4 h before radiation. Mice are sacrificed to collect small intestines for histology analysis and western blotting. All mice are injected i.p. with 100 mg/kg of BrdU before sacrifice.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

CUSTOMER VALIDATION

- Nat Med. 2016 May;22(5):547-56.
- Mil Med Res. 2020 Sep 6;7(1):42.
- Cell Stem Cell. 2022 Sep 1;29(9):1366-1381.e9.
- Cell Stem Cell. 2022 Jul 7;29(7):1102-1118.e8.
- Mol Cell. 2022 Jun 3;S1097-2765(22)00480-4.

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REFERENCES

- [1]. Ring DB, et al. Selective glycogen synthase kinase 3 inhibitors potentiate insulin activation of glucose transport and utilization in vitro and in vivo. *Diabetes*. 2003 Mar;52(3):588-95.
- [2]. Bennett CN, et al. Regulation of Wnt signaling during adipogenesis. *J Biol Chem*. 2002 Aug 23;277(34):30998-1004.
- [3]. Naujok O, et al. Cytotoxicity and activation of the Wnt/beta-catenin pathway in mouse embryonic stem cells treated with four GSK3 inhibitors. *BMC Res Notes*. 2014 Apr 29;7:273.
- [4]. Wang X, et al. Pharmacologically blocking p53-dependent apoptosis protects intestinal stem cells and mice from radiation. *Sci Rep*. 2015 Apr 10;5:8566.
- [5]. Ye S, et al. Pleiotropy of glycogen synthase kinase-3 inhibition by CHIR99021 promotes self-renewal of embryonic stem cells from refractory mouse strains. *PLoS One*. 2012;7(4):e35892.
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Caution: Product has not been fully validated for medical applications. For research use only.

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