YM-244769 dihydrochloride

Cat. No.: HY-136182

CAS No.: 1780390-65-9

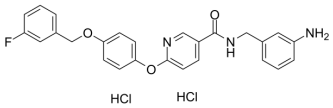
Molecular Formula: $C_{26}H_{24}Cl_2FN_3O_3$

Molecular Weight: 516.39

Target: Na+/Ca2+ Exchanger

Pathway: Membrane Transporter/Ion Channel

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 : 100 mg/mL (193.65 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9365 mL	9.6826 mL	19.3652 mL
	5 mM	0.3873 mL	1.9365 mL	3.8730 mL
	10 mM	0.1937 mL	0.9683 mL	1.9365 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.03 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.03 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

YM-244769 dihydrochloride is a potent, selective and orally active Na^+/Ca^{2+} exchanger (NCX) inhibitor. YM-244769 dihydrochloride preferentially inhibits NCX3 and suppresses the unidirectional outward NCX current (Ca^{2+} entry mode), with IC_{50}s of 18 nM and 50 nM, respectively. YM-244769 dihydrochloride efficiently protects against hypoxia/reoxygenation-induced SH-SY5Y neuronal cell damage. YM-244769 dihydrochloride can also increase urine volume and urinary excretion of electrolytes in mice[1][2][3].

IC_{50} & Target

IC_{50}: 18 nM (NCX3), 68 nM (NCX1), 96 nM (NCX2)[1]

In Vitro

YM-244769 (0.003-1 μM) inhibits dose dependently the initial rates of $^{45}Ca^{2+}$ uptake into NCX1, NCX2, and NCX3 transfectants with IC_{50} values of 68 ± 2.9, 96 ± 3.5, and 18 ± 1.0 nM, respectively[1].
YM-244769 (0.3 or 1 μM) efficiently protects against the hypoxia/reoxygenation-induced lactate dehydrogenase (LDH) release

in SH-SY5Y cells and in LLC-PK_1 cells (1 μM)[1].
YM-244769 possesses reverse mode-selectivity[1].
YM-244769 (1 and 10 μM) inhibits NCX current (I_{NCX}) in a concentration- and $[Na^+]_i$-dependent manner, the IC_{50} against the unidirectional outward I_{NCX} (Ca^{2+} entry mode) is 0.05 μM. The IC_{50} values against the bidirectional outward and inward I_{NCX} are similar and approximately 100 nM with a Hill coefficient of about 1[3].
YM-244769 is trypsin-insensitive[3].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	SH-SY5Y cells treated with NCX1 or NCX3 antisense
Concentration:	0.3 and 1 μM
Incubation Time:	
Result:	Hypoxia/reoxygenation-induced LDH release was significantly attenuated: reduction in cell damage was greater in cells treated with NCX3 antisense (by 61%) than in cells treated with NCX1 antisense (by 35%). 0.3 or 1 μM efficiently suppressed the hypoxia/reoxygenation-induced cell damage in SH-SY5Y cells treated with NCX1 antisense more than in those treated with NCX3 antisense.

In Vivo

YM-244769 (0.1-1 mg/kg; p.o.; once) exhibits dose-dependently natriuretic action in mice and significantly increases urinary excretion of Ca^{2+} as well as Ca^{2+}/Cr ratio[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Wild-type C57BL/6J mice and NCX-KO mice[2]
Dosage:	0.1, 0.3 and 1 mg/kg
Administration:	Oral administration, once
Result:	Caused a dose-dependent increase (up to approximately 200%) in urine volume and urinary excretion of electrolytes (Na^+, K^+ and Cl^-). Natriuretic actions were equivalently observed in NCX1-KO and WT, but disappeared in NCX2-KO and double KO.

REFERENCES

[1]. Gotoh Y, et al. Genetic knockout and pharmacologic inhibition of NCX2 cause natriuresis and hypercalciuria. Biochem Biophys Res Commun. 2015 Jan 9;456(2):670-5.

[2]. Yamashita K, et al. Inhibitory effect of YM-244769, a novel Na+/Ca2+ exchanger inhibitor on Na+/Ca2+ exchange current in guinea pig cardiac ventricular myocytes. Naunyn Schmiedebergs Arch Pharmacol. 2016 Nov;389(11):1205-1214.

[3]. Takahiro Iwamoto , et al. YM-244769, a Novel Na^+/Ca^{2+} Exchange Inhibitor That Preferentially Inhibits NCX3, Efficiently Protects Against hypoxia/reoxygenation-induced SH-SY5Y Neuronal Cell Damage. Mol Pharmacol. 2006 Dec;70(6):2075-

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