SB-743921 hydrochloride

Cat. No.: HY-12069

CAS No.: 940929-33-9

Molecular Formula: $C_{31}H_{34}Cl_2N_2O_3$

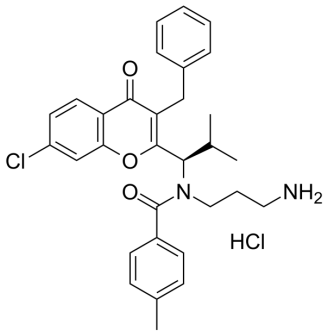
Molecular Weight: 553.52

Target: Kinesin

Pathway: Cell Cycle/DNA Damage; Cytoskeleton

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 : ≥ 100 mg/mL (180.66 mM)

H_2O : 10 mg/mL (18.07 mM; ultrasonic and warming and heat to 60°C)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent \ Mass	1 mg	5 mg	10 mg
1 mM	1.8066 mL	9.0331 mL	18.0662 mL
5 mM	0.3613 mL	1.8066 mL	3.6132 mL
10 mM	0.1807 mL	0.9033 mL	1.8066 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: ≥ 2.5 mg/mL (4.52 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.52 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.52 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

SB-743921 hydrochloride is a potent inhibitor of the mitotic kinesin KSP (Eg5), with a K_i of 0.1 nM.

IC_{50} & Target

Eg5

0.1 nM (Ki)

In Vitro	SB-743921 is a potent inhibitor of Eg5, with a K_i of 0.1 nM[1]. SB-743921 (1 nM) potently inhibits colony forming cell (CFC) formation of chronic myeloid leukemia (CML) primary cells, but exhibits slight inhibitory activities on the colony-forming ability of normal bone marrow progenitors. SB-743921 (1, 3 nM) induces apoptosis of CML primary CD34 + cells, and shows slight effect on normal CD34 + cells. SB-743921 (2 nM) in combination with imatinib displays additive anti-proliferative effect in KCL22 and CML CD34 + cells. Furthermore, SB-743921 overcomes imatinib resistance in CML cells. SB-743921 (0.5 nM, 1 nM, 3 nM) inhibits MEK/ERK and AKT signaling in CML cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	SB-743921 has good oral bioavailability and pharmacokinetics and induces complete tumor regression in nude mice bearing lung cancer patient xenografts[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	K562 and KCL22 cells are seeded in six-well plates at a number of 5×10^5 in 2 mL RPMI-1640 medium supplemented with 10% FBS in a 5% CO_2 atmosphere at 37°C, and are treated with control (2% DMSO), 50 nM imatinib, 2 nM SB-743921 and 50 nM imatinib + 2 nM SB-743921, respectively. Cell number and viability are determined every 24 h. Results are plotted for live cells against time to generate a growth curve[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	The animal experiments are performed with female NMRI nu/nu mice. Tumor fragments are obtained from xenografts in serial passage in nude mice. Mice are randomized to the various groups, and dosing is started when the required number of mice carries a tumor of 50-250 mm^3 volume, preferably 80-200 mm^3. Vehicle for 1: 10% ethanol, 10% cremophor, 80% D5W (dextrose 5%); vehicle for all other compounds (including SB-743921): 8% DMSO, 2% Tween 80, distilled water (pH 5). All treatments are given intraperitoneally. Vehicle control mice (group 1) are treated with 10 mL/kg vehicle on days 0, 3, 6, 8, 10, 13, 20, 22, 24, 29, 31, 34, 36, 38, 48, 51, 55, 58, 62, 65, and 69[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Jeffrey R. Jackson, et al. A second generation KSP inhibitor, SB-743921, is a highly potent and active therapeutic in preclinical models of cancer. First AACR International Conference on Molecular Diagnostics in Cancer Therapeutic Development, Sep 12-15, 2006.

[2]. Yin Y, et al. Kinesin spindle protein inhibitor SB743921 induces mitotic arrest and apoptosis and overcomes imatinib resistance of chronic myeloid leukemia cells. Leuk Lymphoma. 2015 Jun;56(6):1813-20.

[3]. Good JA, et al. Optimized S-trityl-L-cysteine-based inhibitors of kinesin spindle protein with potent in vivo antitumor activity in lung cancer xenograft models. J Med Chem. 2013 Mar 14;56(5):1878-93.

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