K858 (Racemic)

Cat. No.: HY-19966

CAS No.: 72926-24-0

Molecular Formula: $C_{13}H_{15}N_3O_2S$

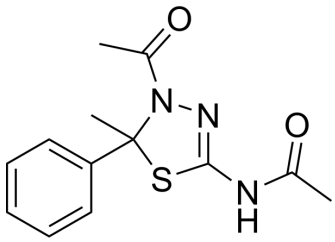
Molecular Weight: 277.34

Target: Kinesin; Apoptosis

Pathway: Cell Cycle/DNA Damage; Cytoskeleton; Apoptosis

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 (360.57 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.6057 mL	18.0284 mL	36.0568 mL
5 mM	0.7211 mL	3.6057 mL	7.2114 mL
10 mM	0.3606 mL	1.8028 mL	3.6057 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 (9.01 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (9.01 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

K858 Racemic is an ATP-uncompetitive inhibitor of kinesin Eg5 with an IC_{50} of 1.3 μM.

IC_{50} & Target

Eg5
1.3 μM (IC_{50})

In Vitro

K858 Racemic is an ATP-uncompetitive inhibitor of Eg5 with an IC_{50} of 1.3 μM. K858 does not inhibit the ATPase activity of the mitotic kinesins CENP-E and MKLP1, or the conventional kinesin heavy chain even at 200 μM. K858 induces mitotic arrest and growth inhibition via the activation of the Mad2-mediated spindle checkpoint. K858 (5 μM) induces mitotic cell death in cancer cells but not in normal cells[1]. K858 (1, 10, 100 μM) inhibits the MCF7, BT474 and SKBR3 cell lines, and only at 10 and 100 μM suppresses MDA-MB231 cell line after treatment for 24 h. K858 incereases Bax/Bcl2 RNA ratio and survivin in the four

	cell lines. Furthermore, the up-regulation of survivin is totally reversed by wortmannin (phosphoinositide 3-kinase AKT) in MCF7 cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	K858 (50, 150 mg/kg, p.o.) shows antitumor activity in an A2780 ovarian cancer xenograft model, also inhibits tumor grwoth in a HCT116 colon cancer xenograft model via 100 mg/kg twice a day orally for 5 days. K858 (100 mg/kg, p.o., qd ×5) displays no neurotoxic side effects in mice[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	To determine cytotoxicity, sulforhodamine B colorimetric assay is performed: 1.5×10^4 cells are plated on 96 well plates, grown for 24 h (h) and treated with different concentrations of K858 (1 μM, 10 μM, 100 μM) for 24 and 48 h. Cells are then fixed with 50 % trichloroacetic acid for 1 h at 4°C and stained for 30 min at room temperature (RT) with 0.4 % sulforhodamine B in 1 % acetic acid. Excess dye is removed by washing four times with 1 % acetic acid. Protein bound dye is dissolved in 10 mM TRIS pH 10, and optical density (OD) is determined at 510 nm using a microplate reader[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	A2780 cells (5×10^6 cells) are inoculated s.c. into BALB/cAJcl-nu mice. K858 is administered orally twice daily on days 0 to 4, and 7 to 11 at 150 and 50 mg/kg. Doses and schedules are determined by the tolerability studies performed in advance. Vehicle (0.5% methylcellulose 400) is administered orally as a control twice daily on days 0 to 4, and 7 to 11. Paclitaxel is administered i.v. on day 0 at 25 mg/kg. Carboplatin is administered i.v. on day 0 at 60 mg/kg. Drug efficacy is expressed as the ratio of the mean experimental V/V0 value to that of the control group [treated versus control (T/C) ratio], where V is the tumor volume at the day of evaluation and V0 is the tumor volume at the day of the initial treatment with the drug. Statistical analysis is performed using the nonparametric rank-sum test[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Nakai R, et al. K858, a novel inhibitor of mitotic kinesin Eg5 and antitumor agent, induces cell death in cancer cells. Cancer Res. 2009 May 1;69(9):3901-9.

[2]. De Iuliis F, et al. The kinesin Eg5 inhibitor K858 induces apoptosis but also survivin-related chemoresistance in breast cancer cells. Invest New Drugs. 2016 Aug;34(4):399-406.

Caution: Product has not been fully validated for medical applications. For research use only.

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