Prexasertib dimesylate

Cat. No.: HY-18174E

CAS No.: 1234015-58-7

Molecular Formula: $C_{20}H_{27}N_7O_8S_2$

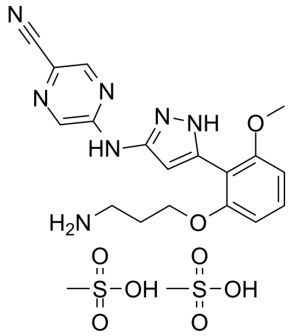
Molecular Weight: 557.6

Target: Checkpoint Kinase (Chk); Apoptosis

Pathway: Cell Cycle/DNA Damage; Apoptosis

Storage: 4°C, stored under nitrogen

* In solvent : -80°C, 6 months; -20°C, 1 month (stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (179.34 mM; Need ultrasonic)

H_2O : 50 mg/mL (89.67 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7934 mL	8.9670 mL	17.9340 mL
5 mM	0.3587 mL	1.7934 mL	3.5868 mL
10 mM	0.1793 mL	0.8967 mL	1.7934 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: ≥ 3.5 mg/mL (6.28 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 3.5 mg/mL (6.28 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Prexasertib dimesylate (LY2606368 dimesylate) is a selective, ATP-competitive second-generation checkpoint kinase 1 (CHK1) inhibitor with a K_i of 0.9 nM and an IC_{50} of <1 nM. Prexasertib dimesylate inhibits CHK2 (IC_{50}=8 nM) and RSK1 (IC_{50}=9 nM). Prexasertib dimesylate causes double-stranded DNA breakage and replication catastrophe resulting in apoptosis. Prexasertib dimesylate shows potent anti-tumor activity[1][2].

IC_{50} & Target			
	Chk1 0.9 nM (Ki)	Chk1 <1 nM (IC_{50})	Chk2 8 nM (IC_{50})

In Vitro

Prexasertib dimesylate (LY2606368 dimesylate) inhibits MELK (IC_{50}=38 nM), SIK (IC_{50}=42 nM), BRSK2 (IC_{50}=48 nM), ARK5 (IC_{50}=64 nM). Prexasertib dimesylate requires CDC25A and CDK2 to cause DNA damage[1].

Prexasertib dimesylate (33, 100 nM; for 7 hours) results in DNA damage during S-phase in HeLa cells[1].
Prexasertib dimesylate (8-250 nM; pre-treated for 15 minutes) inhibits CHK1 autophosphorylation (S296) and CHK2 autophosphorylation (S516) in HT-29 cells[1].
Prexasertib dimesylate (4 nM; 24 hours) results in a large shift in cell-cycle populations from G1 and G2-M to S-phase with an accompanied induction of H2AX phosphorylation in U-2 OS cells[1].
Prexasertib dimesylate (33 nM; for 12 hours) causes chromosomal fragmentation in HeLa cells. Prexasertib dimesylate (100 nM; 0.5 to 9 hours) induces replication stress and depletes the pool of available RPA2 for binding to DNA[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Cycle Analysis[1]

Cell Line:	HeLa cells
Concentration:	33, 100 nM
Incubation Time:	For 7 hours
Result:	Had an IC_{50} of 37 nM and resulted in the G2-M population received DNA damage during S-phase but continued to progress through the cell cycle into an early mitosis.

Western Blot Analysis[1]

Cell Line:	HT-29 cells
Concentration:	8, 16, 31, 63, 125, 250 nM
Incubation Time:	Pre-treated for 15 minutes
Result:	Inhibited CHK1 autophosphorylation (S296) and CHK2 autophosphorylation (S516) (IC_{50} of less than 31 nM) in HT-29 cells.

In Vivo

Prexasertib dimesylate (LY2606368 dimesylate; 1-10 mg/kg; SC; twice daily for 3 days, rest 4 days; for three cycles) causes growth inhibition in tumor xenografts[1].
Prexasertib dimesylate (15 mg/kg; SC) causes CHK1 inhibition in the blood and the phosphorylation of both H2AX (S139) and RPA2 (S4/S8)[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Female CD-1 nu-/nu- mice (26-28 g) with Calu-6 cells[1]
Dosage:	1, 3.3, or 10 mg/kg
Administration:	SC; twice daily for 3 days, rest 4 days; for three cycles
Result:	Caused statistically significant tumor growth inhibition (up to 72.3%).

Animal Model:	Female CD-1 nu-/nu- mice (26-28 g) with Calu-6 cells[1]
Dosage:	15 mg/kg (Pharmacokinetic Analysis)
Administration:	SC (200 μL)
Result:	CHK1 was 7 ng/mL at 12 hours and 3 ng/mL by 24 hours in plasma exposures. Phosphorylation of both H2AX (S139) and RPA2 (S4/S8) was detectable at 4 hours, showing the rapid occurrence of DNA damage.

CUSTOMER VALIDATION

- Nat Commun. 2019 Aug 2;10(1):3485.
- Thorax. 2021 Jul 5;thoraxjnl-2021-217377.
- Oncogene. 2022 Oct 12.
- Cell Biol Toxicol. 2021 Sep 14.
- Cancers (Basel). 2021 Aug 20;13(16):4200.

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REFERENCES

[1]. King C, et al. LY2606368 Causes Replication Catastrophe and Antitumor Effects through CHK1-Dependent Mechanisms. Mol Cancer Ther. 2015 Sep;14(9):2004-1

[2]. Yin Y, et al. Chk1 inhibition potentiates the therapeutic efficacy of PARP inhibitor BMN673 in gastric cancer. Am J Cancer Res. 2017 Mar 1;7(3):473-483.

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