Prexasertib dihydrochloride

Cat. No.: HY-18174A

CAS No.: 1234015-54-3

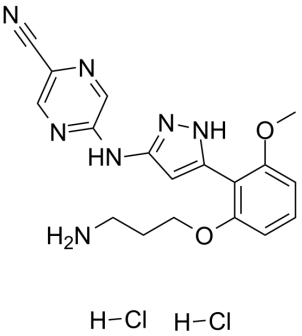
Molecular Formula: $C_{18}H_{21}Cl_2N_7O_2$

Molecular Weight: 438.31

Target: Checkpoint Kinase (Chk); Apoptosis

Pathway: Cell Cycle/DNA Damage; Apoptosis

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 : 8 mg/mL (18.25 mM; Need ultrasonic)
H_2O : 1 mg/mL (2.28 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2815 mL	11.4075 mL	22.8149 mL
5 mM	0.4563 mL	2.2815 mL	4.5630 mL
10 mM	0.2281 mL	1.1407 mL	2.2815 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: ≥ 0.8 mg/mL (1.83 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.8 mg/mL (1.83 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Prexasertib dihydrochloride (LY2606368 dihydrochloride) 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 dihydrochloride inhibits CHK2 (IC_{50}=8 nM) and RSK1 (IC_{50}=9 nM). Prexasertib dihydrochloride causes double-stranded DNA breakage and replication catastrophe resulting in apoptosis. Prexasertib dihydrochloride shows potent anti-tumor activity[1][2].

IC_{50} & Target

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

In Vitro

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

Prexasertib dihydrochloride (33, 100 nM; for 7 hours) results in DNA damage during S-phase in HeLa cells[1].
Prexasertib dihydrochloride (8-250 nM; pre-treated for 15 minutes) inhibits CHK1 autophosphorylation (S296) and CHK2 autophosphorylation (S516) in HT-29 cells[1].
Prexasertib dihydrochloride (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 dihydrochloride (33 nM; for 12 hours) causes chromosomal fragmentation in HeLa cells. Prexasertib (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 dihydrochloride (LY2606368 dihydrochloride; 1-10 mg/kg; SC; twice daily for 3 days, rest 4 days; for three cycles) causes growth inhibition in tumor xenografts[1].
Prexasertib dihydrochloride (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.
- Cell Biol Toxicol. 2021 Sep 14.
- Cancers (Basel). 2021 Aug 20;13(16):4200.
- Cancers. 2020 Aug 26;12(9):2426.

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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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