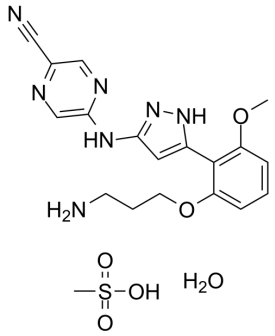
Prexasertib Mesylate Hydrate



Cat. No.:	HY-18174B
CAS No.:	1234015-57-6
Molecular Formula:	$C_{19}H_{25}N_7O_6S$
Molecular Weight:	479.51
Target:	Checkpoint Kinase (Chk); Apoptosis
Pathway:	Cell Cycle/DNA Damage; Apoptosis
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.

BIOLOGICAL ACTIVITY

Description	Prexasertib Mesylate Hydrate (LY2606368 Mesylate Hydrate) 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 Mesylate Hydrate inhibits CHK2 (IC_{50}=8 nM) and RSK1 (IC_{50}=9 nM). Prexasertib Mesylate Hydrate causes double-stranded DNA breakage and replication catastrophe resulting in apoptosis. Prexasertib Mesylate Hydrate 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 Mesylate Hydrate (LY2606368 Mesylate Hydrate) 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 Mesylate Hydrate (33, 100 nM; for 7 hours) results in DNA damage during S-phase in HeLa cells[1].

Prexasertib Mesylate Hydrate (8-250 nM; pre-treated for 15 minutes) inhibits CHK1 autophosphorylation (S296) and CHK2 autophosphorylation (S516) in HT-29 cells[1].

Prexasertib Mesylate Hydrate (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 Mesylate Hydrate (33 nM; for 12 hours) causes chromosomal fragmentation in HeLa cells. Prexasertib Mesylate Hydrate (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 Mesylate Hydrate (LY2606368 Mesylate Hydrate; 1-10 mg/kg; SC; twice daily for 3 days, rest 4 days; for three cycles) causes growth inhibition in tumor xenografts[1].
Prexasertib Mesylate Hydrate (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):2004-13.

[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.

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

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