



上海源叶生物科技有限公司
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产品名称: **PHA-767491 (hydrochloride)**

产品别名: **CAY-10572 hydrochloride**

生物活性:

Description	PHA-767491 hydrochloride is a dual Cdc7/Cdk9 inhibitor, with IC50s of 10 nM and 34 nM, respectively.				
IC ₅₀ & Target	CDK9	CDK2	CDK1	CDK5	GSK3-β
	34 nM (IC ₅₀)	240 nM (IC ₅₀)	250 nM (IC ₅₀)	460 nM (IC ₅₀)	220 nM (IC ₅₀)
	Mk2	Plk1	Chk2		
	470 nM (IC ₅₀)	980 nM (IC ₅₀)	1100 nM (IC ₅₀)		
In Vitro	PHA-767491 inhibits proliferation in both cell lines with an IC50 of 0.64 μM in HCC1954 cells and 1.3 μM in Colo-205 cells. PHA-767491 is effective DDK inhibitors in vitro, with IC50 values of 18.6 nM. PHA-767491 (2 μM) completely abolishes Mcm2 phosphorylation by 24 hours in HCC1954 cells[1]. PHA-767491 in combination with 5-FU exhibits much stronger cytotoxicity and induces significant apoptosis manifested by remarkably increased caspase 3 activation and poly(ADP-Ribose) polymerase fragmentation in HCC cells. PHA-767491 directly counteracts the 5-FU-induced phosphorylation of Chk1 and decreases the expression of the anti-apoptotic protein myeloid leukemia cell 1ine[2]. PHA-767491 (0-10 μM) decreases glioblastoma cell viability in a time- and dose-dependent fashion, with IC50 of approximately 2.5 μM for U87-MG and U251-MG cells. PHA-767491 hydrochloride induces apoptosis in glioblastoma cells, suppresses glioblastoma cell proliferation, cell migration and cell invasion[3].				
In Vivo	PHA-767491 decreases Chk1 phosphorylation and increases in situ cell apoptosis in tumor tissues sectioned from nude mice HCC xenografts[2].				
Solvent&Solubility	In Vitro: H₂O : 50 mg/mL (200.24 mM; Need ultrasonic) DMSO : 17.33 mg/mL (69.40 mM; Need ultrasonic and warming)				
		SolventMassConcentration	1 mg	5 mg	10 mg
	Preparing	1 mM	4.0048 mL	20.0240 mL	40.0481 mL
	Stock Solutions	5 mM	0.8010 mL	4.0048 mL	8.0096 mL
		10 mM	0.4005 mL	2.0024 mL	4.0048 mL
	*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液; 一旦配成溶液, 请分装保存, 避免反复冻融造成的产品失效。 储备液的保存方式和期限 -80°C, 6 months; -20°C, 1 month。 -80°C 储存时, 请在 6 个月内使用, -20°C 储存时, 请在 1 个月内使用。 In Vivo: 请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液, 再依次添加助溶剂: ——为保证实验结果的可靠性, 澄清的储备液可以根据储存条件, 适当保存; 体内实验的工作液, 建议您现用现配, 当天使用; 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比; 如在配制过程中出现沉淀、析出现象, 可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂: 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline				



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	Solubility: ≥ 1 mg/mL (4.00 mM); Clear solution 此方案可获得 ≥ 1 mg/mL (4.00 mM, 饱和度未知) 的澄清溶液。 以 1 mL 工作液为例, 取 100 μL 10.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中, 混合均匀向上述体系中加入 50 μL Tween-80, 混合均匀; 然后继续加入 450 μL 生理盐水定容至 1 mL。 2. 请依序添加每种溶剂: 10% DMSO $\rightarrow$ 90% (20% SBE-β-CD in saline) Solubility: ≥ 1 mg/mL (4.00 mM); Clear solution 此方案可获得 ≥ 1 mg/mL (4.00 mM, 饱和度未知) 的澄清溶液。 以 1 mL 工作液为例, 取 100 μL 10.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中, 混合均匀。
References	[1]. Sasi NK, et al. The potent Cdc7-Dbf4 (DDK) kinase inhibitor XL413 has limited activity in many cancer cell lines and discovery of potential new DDK inhibitor scaffolds. PLoS One. 2014 Nov 20;9(11):e113300. [2]. Li W, et al. Dual Inhibition of Cdc7 and Cdk9 by PHA-767491 Suppresses Hepatocarcinoma Synergistically with 5-Fluorouracil. Curr Cancer Drug Targets. 2015;15(3):196-204. [3]. Erbayraktar Z, et al. Cell division cycle 7-kinase inhibitor PHA-767491 hydrochloride suppresses glioblastoma growth and invasiveness. Cancer Cell Int. 2016 Nov 18;16:88. [4]. Montagnoli A, et al. A Cdc7 kinase inhibitor restricts initiation of DNA replication and has antitumor activity. Nat Chem Biol. 2008 Jun;4(6):357-65. [5]. Montagnoli A, et al. A Cdc7 kinase inhibitor restricts initiation of DNA replication and has antitumor activity. Nat Chem Biol. 2008 Jun;4(6):357-65.
实验参考:	
Cell Assay	For assays in 96 well plates 2500 cells are plated per well. After 24 hours, cells are treated with small molecule inhibitors and incubated for 72 hours at 37°C. Subsequently the cells are lysed and the ATP content is measured as an indicator of metabolically active cells using the CellTiter-Glo assay. IC₅₀ values are calculated using the GraphPad software. For assays in six well plates, 100,000 cells are plated per well. After 24 hours, cells are treated with small molecule inhibitors and incubated for varying time points. Cells are trypsinized and a suspension is made in 5 mL of phosphate buffered saline. 30 μL of this suspension is mixed with 30 μL of CellTiter-Glo reagent followed by a 10-minute incubation at room temperature. Luminescence is measured using EnVision 2104 Multilabel Reader and BioTek Synergy Neo Microplate Reader. [1]
Kinase Assay	20 ng of purified human DDK is pre-incubated with increasing concentrations of each DDK inhibitor for 5 min. Then 10 μCi (γ)-³²P ATP and 1.5 μM cold ATP are added in a buffer containing 50 mM Tris-HCl (pH 7.5), 10 mM MgCl₂, and 1 mM DTT and incubated for 30 min at 30°C. The proteins are denatured in 1X Laemmli buffer at 100°C followed by SDS-PAGE and autoradiography on HyBlot CL film. Auto-phosphorylation of DDK is used as an indicator of its kinase activity. ³²P-labeled bands are quantified using ImageJ and the IC₅₀ values are calculated using GraphPad. [1]
	[1]. Sasi NK, et al. The potent Cdc7-Dbf4 (DDK) kinase inhibitor XL413 has limited activity in many cancer cell lines and discovery of potential new DDK inhibitor scaffolds. PLoS One. 2014 Nov 20;9(11):e113300. [2]. Li W, et al. Dual Inhibition of Cdc7 and Cdk9 by PHA-767491 Suppresses Hepatocarcinoma



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