产品名称：PHA-848125
产品别名：Milciclib

生物活性：

Description	Milciclib (PHA-848125) is a potent, dual inhibitor of CDK and Tropomyosin receptor kinase (TRK), with IC_{50}s of 45, 150, 160, 363, 398 nM and 53 nM for cyclin A/CDK2, cyclin H/CDK7, cyclin D1/CDK4, cyclin E/CDK2, cyclin B/CDK1 and TRKA, respectively.

IC_{50} & Target	cyclin A/CDK2	cyclin E/CDK2	cyclin H/CDK7	cyclin D1/CDK4	cyclin B/CDK1	TRKA
	45 nM (IC_{50})	363 nM (IC_{50})	150 nM (IC_{50})	160 nM (IC_{50})	398 nM (IC_{50})	53 nM (IC_{50})

In Vitro	Milciclib (PHA-848125; 0.156 or 0.625 μM) up-regulates the expression of PDCD4, DDIT4, SESN2/sestrin 2 and DEPDC6/DEPTOR in GL-Mel cells[1]. Milciclib (PHA-848125) potently inhibits the kinase activity of CDK2/cyclin A complex and of TRKA in a biochemical assay, with IC50s of 45 and 53 nM, respectively. Milciclib induces a clear accumulation of cells in G1 phase. Milciclib strongly inhibits NGF-induced phosphorylation of TRKA in a dose-dependent manner[2].
In Vivo	Milciclib (PHA-848125; 5, 10, and 15 mg/kg, p.o.) inhibits the growth of tumor in 7,12-dimethylbenz(a) anthracene (DMBA)-induced rat mammary carcinoma model. Milciclib has significant antitumor activity in various human xenografts and carcinogen-induced tumors as well as in disseminated primary leukemia models, with plasma concentrations in rodents in the same range as those found active in inhibiting cancer cell proliferation[2]. Milciclib (PHA-848125; 40 mg/kg) induces a significant tumor growth inhibition in K-Ras^{G12D} mice, and this is accompanied by a reduction in the cell membrane turnover[3].

Solvent&Solubility

In Vitro:

DMSO： 20 mg/mL (43.42 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1712 mL	10.8561 mL	21.7122 mL
	5 mM	0.4342 mL	2.1712 mL	4.3424 mL
	10 mM	0.2171 mL	1.0856 mL	2.1712 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

Solubility: ≥ 2 mg/mL (4.34 mM); Clear solution

此方案可获得 ≥ 2 mg/mL (4.34 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 20.0 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→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2 mg/mL (4.34 mM); Clear solution 此方案可获得 ≥ 2 mg/mL (4.34 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 20.0 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]. Caporali S, Alvino E, Levati L, Esposito AI, Ciomei M, Brasca MG, Del Bufalo D, Desideri M, Bonmassar E, Pfeffer U, D'Atri S. Down-regulation of the PTTG1 proto-oncogene contributes to the melanoma suppressive effects of the cyclin-dependent kinase inhibitor PHA-848125. Biochem Pharmacol. 2012 Sep 1;84(5):598-611. [2]. Albanese C, Alzani R, Amboldi N, Avanzi N, Ballinari D, Brasca MG, Festuccia C, Fiorentini F, Locatelli G, Pastori W, Patton V, Roletto F, Colotta F, Galvani A, Isacchi A, Moll J, Pesenti E, Mercurio C, Ciomei M. Dual targeting of CDK and tropomyosin receptor kinase families by the oral inhibitor PHA-848125, an agent with broad-spectrum antitumor efficacy. Mol Cancer Ther. 2010 Aug;9(8):2243-54. [3]. Degrassi A, et al. Efficacy of PHA-848125, a cyclin-dependent kinase inhibitor, on the K-Ras(G12D)LA2 lung adenocarcinoma transgenic mouse model: evaluation by multimodality imaging. Mol Cancer Ther. 2010 Mar;9(3):673-81.

实验参考：

Cell Assay	Cells are seeded into 96- or 384-well plates at densities ranging from 10,000 to 30,000/cm^2 in appropriate medium plus 10% FCS. After 24 hours, cells are treated in duplicate with serial dilutions of Milciclib, and 72 hours later, viable cell number is assessed using the CellTiter-Glo Assay. IC_{50}s are calculated using a Sigmoidal fitting algorithm. Experiments are done independently at least twice. [2]
Animal Administration	Rats are randomized and introduced into the study when at least one mammary tumor attained a diameter of 0.5 cm. Groups of 10 animals are treated orally twice a day continuously for 10 days with vehicle (glucosate) or with 5, 10, and 15 mg/kg of Milciclib, whereas a further group receives two cycles of Milciclib at 20 mg/kg orally twice a day for 5 days with an intervening rest period of 1 week. Tumor volume is measured regularly by caliper for the duration of the experiment. [2]
References	[1]. Caporali S, Alvino E, Levati L, Esposito AI, Ciomei M, Brasca MG, Del Bufalo D, Desideri M, Bonmassar E, Pfeffer U, D'Atri S. Down-regulation of the PTTG1 proto-oncogene contributes to the melanoma suppressive effects of the cyclin-dependent kinase inhibitor PHA-848125. Biochem Pharmacol. 2012 Sep 1;84(5):598-611. [2]. Albanese C, Alzani R, Amboldi N, Avanzi N, Ballinari D, Brasca MG, Festuccia C, Fiorentini F, Locatelli G, Pastori W, Patton V, Roletto F, Colotta F, Galvani A, Isacchi A, Moll J, Pesenti E, Mercurio C, Ciomei M. Dual targeting of CDK and tropomyosin receptor kinase families by the oral inhibitor PHA-848125, an agent with broad-spectrum antitumor efficacy. Mol Cancer Ther. 2010 Aug;9(8):2243-54. [3]. Degrassi A, et al. Efficacy of PHA-848125, a cyclin-dependent kinase inhibitor, on the K-Ras(G12D)LA2 lung adenocarcinoma transgenic mouse model: evaluation by multimodality imaging. Mol Cancer Ther. 2010 Mar;9(3):673-81.