Milciclib

Cat. No.: HY-10424

CAS No.: 802539-81-7

Molecular Formula: $C_{25}H_{32}N_8O$

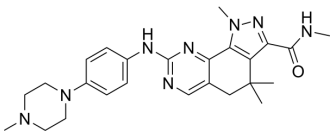
Molecular Weight: 460.57

Target: CDK; Autophagy

Pathway: Cell Cycle/DNA Damage; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



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

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: ≥ 2 mg/mL (4.34 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2 mg/mL (4.34 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Milciclib (PHA-848125) is a potent, ATP-competitive and 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 45 nM (IC_{50})	cyclin E/CDK2 363 nM (IC_{50})	cyclin H/CDK7 150 nM (IC_{50})	cyclin D1/CDK4 160 nM (IC_{50})
cyclin B/CDK1 398 nM (IC_{50})	TRKA 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 IC_{50}s 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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}LA2 mice, and this is accompanied by a reduction in the cell membrane turnover[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- J Exp Med. 2022 Jan 3;219(1):e20210789.
- Sci Rep. 2021 Mar 8;11(1):5374.
- Sci Rep. 2020 Jul 17;10(1):11921.
- Technical University of Munich. 24.01.2018.

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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.

[4]. Brasca, M.G., et al. Identification of N,1,4,4-tetramethyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (PHA-848125), a potent, orally available cyclin dependent kinase inhibitor. J. Med. Chem. 52(16), 5152-5163 (2009).

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