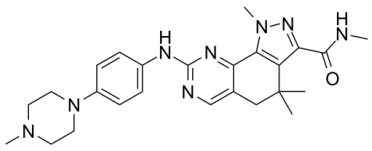
Data Sheet

Product Name:	Milciclib
Cat. No.:	CS-0579
CAS No.:	802539-81-7
Molecular Formula:	C25H32N8O
Molecular Weight:	460.57
Target:	Autophagy; CDK
Pathway:	Autophagy; Cell Cycle/DNA Damage
Solubility:	DMSO : 20 mg/mL (43.42 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 45 nM (cyclin A/CDK2), 150 nM (cyclin H/CDK7), 160 nM (cyclin D1/CDK4), 363 nM (cyclin E/CDK2), 398 nM (cyclin B/CDK1)[1], 53 nM (TRKA)[2] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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. **Animal Administration:** Milciclib is formulated in glucosate.[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.

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.

CAIndexNames:

1H-Pyrazolo[4,3-h]quinazoline-3-carboxamide, 4,5-dihydro-N,1,4,4-tetramethyl-8-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-

SMILES:

O=C(NC)C1=NN(C2=C1C(C)(CC3=CN=C(N=C23)NC4=CC=C(C=C4)N5CCN(CC5)C)C)C

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