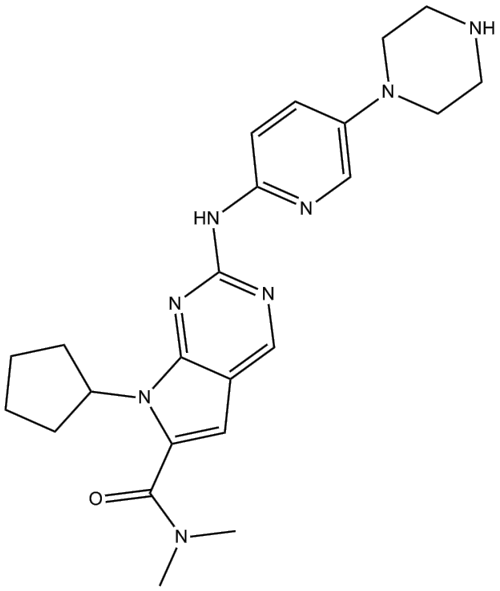
Product Data Sheet

Product Name: LEE011
Cat. No.: GC10842

Chemical Properties

Cas. No.	1211441-98-3		
Chemical Name	7-cyclopentyl-N,N-dimethyl-2-[(5-piperazin-1-ylpyridin-2-yl)amino]pyrrolo[2,3-d]pyrimidine-6-carboxamide		
SMILES	CN(C)C(=O)C1=CC2=CN=C(N=C2N1C3CCCC3)NC4=NC=C(C=C4)N5CCNCC5		
Formula	$C_{23}H_{30}N_8O$	M.Wt	434.54
Solubility	≥ 10.88mg/mL in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

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Cell experiment [1]:

Cell lines	liposarcoma cells
Preparation Method	Cells were collected after exposure to LEE011 or 0.1% DMSO for 24 hours. After washing with ice-cold PBS, the cells were fixed in 70% ethanol at 4°C for at least 2 hours. The fixed cells were then stained in the dark with a PBS solution containing 10μg/mL RNase A and 20μg/mL propidium iodide.
Reaction Conditions	0-3.33μM; 24h
Applications	LEE011 reduced RB phosphorylation at Ser780 and Ser807/811 in both a concentration- and time-dependent manner with complete inhibition at 3.33μM.

Animal experiment [1]:

Animal models	Patient-derived human liposarcoma xenograft models
Preparation Method	Established LP6 cell line xenograft tumors in mice were randomly divided into statistically equivalent groups, and each group was orally administered 250mg/kg LEE011 or a vehicle control daily for 21 days. Tumor size was measured every 3 to 6 days using a caliper. Mouse body weight was recorded every 3 to 7 days.
Dosage form	250mg/kg; po; 21d

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Applications	Oral administration of LEE011 to mice bearing human liposarcoma xenografts resulted in an approximately 50% reduction in tumor uptake of ^{18}F-fluorodeoxyglucose, accompanied by a decrease in tumor biomarkers (including RB phosphorylation and bromodeoxyuridine incorporation). Continuous treatment inhibited tumor growth or induced tumor regression without adversely affecting the mice's body weight. After prolonged continuous administration, a restoration of normal RB phosphorylation and cell cycle progression was observed.

References:

[1]. Zhang Y X, Sicinska E, Czaplinski J T, et al. Antiproliferative effects of CDK4/6 inhibition in CDK4-amplified human liposarcoma in vitro and in vivo[J]. Molecular cancer therapeutics, 2014, 13(9): 2184-2193.

Background

LEE011 is an ATP-competitive and orally active CDK4/6 inhibitor with IC50 values of 10nM and 39nM[1]. LEE011 inhibits the phosphorylation of retinoblastoma protein, thereby preventing CDK-mediated G1-S phase transition, causing cell cycle arrest in the G1 phase, inhibiting DNA synthesis, and suppressing cancer cell growth [2]. LEE011 is commonly used in targeted therapy research for hormone receptor-positive breast cancer and other solid tumors [3].

In three leukemia cell lines, MV4-11, HL-60, and NB4, LEE011(2-5μM;72-48h) significantly induced G1 phase cell cycle arrest in acute leukemia cells [4]. In neuroendocrine tumor cell lines (BON1, QGP1, NCI-H727, and GOT1), LEE011 (500nM; 72h) protects NET cells from DNA damage-induced apoptosis by blocking PARP cleavage and caspase-3/7 activity [5].

In the JeKo-1 xenograft model in nude mice, LEE011 (30-125mg/kg; po; 5d) induces robust inhibition of tumor growth in vivo, concomitant with on-target myelosuppression [6]. In the MOLT4 orthotopic mouse model, LEE011 (75mg/kg; po; 5d) showed a decrease in spleen weight after 5 days of treatment [7]. In patient-derived human liposarcoma xenograft models, oral administration of LEE011(250mg/kg; po; 21d) to mice bearing human liposarcoma xenografts resulted in an

approximately 50% reduction in tumor uptake of ^{18}F-fluorodeoxyglucose, accompanied by a decrease in tumor biomarkers (including RB phosphorylation and bromodeoxyuridine incorporation). Sustained treatment with LEE011 suppresses tumor growth or induces tumor regression while showing no adverse impact on body weight in mice. Following prolonged continuous administration, restoration of RB phosphorylation and cell cycle progression was observed [8].

References:

[1]. VanArsdale T, Boshoff C, Arndt K T, et al. Molecular pathways: targeting the cyclin D–CDK4/6 axis for cancer treatment[J]. Clinical cancer research, 2015, 21(13): 2905-2910.
[2]. Dickson M A. Molecular pathways: CDK4 inhibitors for cancer therapy[J]. Clinical cancer research, 2014, 20(13): 3379-3383.
[3]. Juric D, Munster P N, Campone M, et al. Ribociclib (LEE011) and letrozole in estrogen receptor-positive (ER+), HER2-negative (HER2–) advanced breast cancer (aBC): Phase Ib safety, preliminary efficacy and molecular analysis[J]. 2016.
[4].Tao Y F, Wang N N, Xu L X, et al. Molecular mechanism of G1 arrest and cellular senescence induced by LEE011, a novel CDK4/CDK6 inhibitor, in leukemia cells[J]. Cancer cell international, 2017, 17(1): 35.
[5]. Aristizabal Prada E T, Nölting S, Spoettl G, et al. The novel cyclin-dependent kinase 4/6 inhibitor ribociclib (LEE011) alone and in dual-targeting approaches demonstrates antitumoral efficacy in neuroendocrine tumors in vitro[J]. Neuroendocrinology, 2017, 106(1): 58-73.
[6]. Kim S, Tiedt R, Loo A, et al. The potent and selective cyclin-dependent kinases 4 and 6 inhibitor ribociclib (LEE011) is a versatile combination partner in preclinical cancer models[J]. Oncotarget, 2018, 9(81): 35226.
[7]. Pikman Y, Alexe G, Roti G, et al. Synergistic drug combinations with a CDK4/6 inhibitor in T-cell acute lymphoblastic leukemia[J]. Clinical Cancer Research, 2017, 23(4): 1012-1024.
[8]. Zhang Y X, Sicinska E, Czaplinski J T, et al. Antiproliferative effects of CDK4/6 inhibition in CDK4-amplified human liposarcoma in vitro and in vivo[J]. Molecular cancer therapeutics, 2014, 13(9): 2184-2193.