Ceritinib

Cat. No.: HY-15656

CAS No.: 1032900-25-6

Molecular Formula: $C_{28}H_{36}ClN_5O_3S$

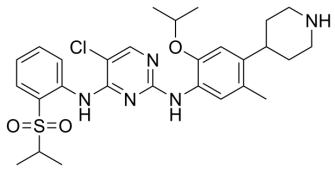
Molecular Weight: 558.14

Target: Anaplastic lymphoma kinase (ALK); Insulin Receptor; IGF-1R

Pathway: Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 12.5 mg/mL (22.40 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7917 mL	8.9583 mL	17.9167 mL
5 mM	0.3583 mL	1.7917 mL	3.5833 mL
10 mM	0.1792 mL	0.8958 mL	1.7917 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: ≥ 0.5 mg/mL (0.90 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.5 mg/mL (0.90 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.5 mg/mL (0.90 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ceritinib (LDK378) is a selective, orally bioavailable, and ATP-competitive ALK tyrosine kinase inhibitor with an IC_{50} of 200 pM. Ceritinib (LDK378) also inhibits IGF-1R, InsR, and STK22D with IC_{50} values of 8, 7, and 23 nM, respectively. Ceritinib (LDK378) shows great antitumor potency[1][2].

IC_{50} & Target

IC50: 0.2 nM (ALK), 7 nM (InsR), 8 nM (IGF-1R), 23 nM (STK22D), 60 nM (FLT3), 260 nM (FGFR2)[1]

In Vitro

Ceritinib (LDK378) also inhibits RET (IC_{50}=400 nM), FGFR3 (IC_{50}=430 nM), LCK (IC_{50}=560 nM), JAK2 (IC_{50}=610 nM), Aurora (IC_{50}

	=660 nM), LYN ($_{50}$=840 nM), EGFR (IC_{50}=900 nM), and FGFR4 (IC_{50}=950 nM)[1]. Ceritinib (LDK378) retains high potency against the ALK enzymatic activity with an IC_{50} value of 200 pM and shows only strong inhibition against IGF-1R, InsR, and STK22D out of a panel of 46 kinases with a minimum selectivity of 70-fold. In Ba/F3 cells transfected with various kinases, Ceritinib inhibits ALK activity with an IC_{50} value of 40.7 nM and had IC_{50} values of >100 nM against all other kinases tested. Ceritinib (LDK378) shows potent antiproliferative activity with an IC_{50} value of 22.8 nM in Karpas 299 human non-Hodgkin's K_i-positive large cell lymphoma carrying the NPM-ALK fusion gene and 26 nM in Ba/F3 cells transfected with the NPM-ALK fusion gene. Ceritinib also shows good selectivity over wild-type Ba/F3 cells (IC_{50} >2 μM) and Ba/F3 cells transfected with Tel-InsR gene (IC_{50}=320 nM)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Ceritinib (LDK378) has an excellent pharmacokinetics profile in rodents and non-rodents with an oral bioavailability of >50%. Ceritinib demonstrates dose-dependent tumor growth inhibition and achieved partial tumor regression in the Karpas 299 rat xenograft model with daily administration but is capable of achieving complete tumor regression in the H2228 NSCLC rat xenograft model, which carries the EML4-ALK fusion gene. In both models, Ceritinib (LDK378) is well tolerated in animals. Ceritinib (LDK378) is further assessed for its ADME profile and is found to have a relatively good metabolic stability in liver microsomes, modest CYP3A4 inhibition, some hERG inhibition with an IC_{50} value of 46 μM in hERG patch clamp experiments, but no evidence of QTc prolongation in both dog and monkey telemetry studies[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	In vivo PK studies are conducted in mice, rats, dogs, and cynomolgus monkeys. Ceritinib (LDK378) (HCl salt) is administered to male Balb/c mice intravenously via tail vein at 5 mg/kg (n=3) and orally via gavage at 20 mg/kg (n=3). By use of the same formulation, Ceritinib (LDK378) (HCl salt) is dosed to Sprague-Dawley rats intravenously via the tail vein at 3 mg/kg (n=3) and orally via gavage at 10 mg/kg (n=3). Blood samples are collected serially at scheduled times over 24 h after dosing. Male beagle dogs receive a single intravenous (n=2) or oral (n=3) dose of Ceritinib (phosphate salt) as an intravenous solution at 5 mg/kg and an oral suspension at 20 mg/kg, respectively. Male cynomologus monkeys receive single intravenous (n=2) or oral (n=3) dose of Ceritinib (free base) as an intravenous solution at 5 mg/kg and an oral suspension at 60 mg/kg, respectively. Blood samples for plasma are collected at prescheduled times over 144 h after dosing[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Cell Discov. 2021 May 11;7(1):33.
- Nat Cancer. 2022 Oct;3(10):1211-1227.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Cell Rep Med. 2023 Jan 10;100911.

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REFERENCES

[1]. Marsilje TH, et al. Synthesis, structure-activity relationships, and in vivo efficacy of the novel potent and selective anaplastic lymphoma kinase (ALK) inhibitor 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (LDK378) currently in phase 1 and phase 2 clinical trials. J Med Chem. 2013 Jul 25;56(14):5675-90.

[2]. Chen J, et al. LDK378: a promising anaplastic lymphoma kinase (ALK) inhibitor. J Med Chem. 2013 Jul 25;56(14):5673-4.

[3]. Tucker ER, et al. Immunoassays for the quantification of ALK and phosphorylated ALK support the evaluation of on-target ALK inhibitors in neuroblastoma. Mol Oncol. 2017 Aug;11(8):996-1006.

[4]. Rothschild SI. Ceritinib-a second-generation ALK inhibitor overcoming resistance in ALK-rearranged non-small celllung cancer. Transl Lung Cancer Res. 2014 Dec;3(6):379-81.

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