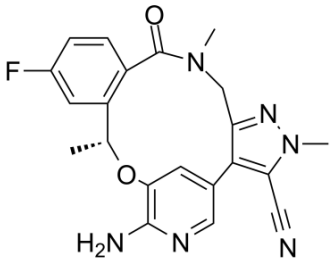
Lorlatinib

Cat. No.:	HY-12215
CAS No.:	1454846-35-5
Molecular Formula:	$C_{21}H_{19}FN_6O_2$
Molecular Weight:	406.41
Target:	ALK; ROS; Apoptosis
Pathway:	Protein Tyrosine Kinase/RTK; Apoptosis
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 28 mg/mL (68.90 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4606 mL	12.3028 mL	24.6057 mL
5 mM	0.4921 mL	2.4606 mL	4.9211 mL
10 mM	0.2461 mL	1.2303 mL	2.4606 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: ≥ 2.5 mg/mL (6.15 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (6.15 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Lorlatinib (PF-06463922) is a selective, orally active, brain-penetrant and ATP-competitive ROS1/ALK inhibitor. Lorlatinib has K_is of <0.025 nM, <0.07 nM, and 0.7 nM for ROS1, wild type ALK, and ALK^{L1196M}, respectively. Lorlatinib has anticancer activity[1][2].

IC_{50} & Target	Ki: < 0.02 nM (ROS1), < 0.07 nM (ALK WT), 0.7 nM (ALK L1196M)
In Vitro	Lorlatinib (PF-06463922) demonstrates significant cell activity against ALK and a large set of ALK clinical mutations with IC_{50} ranging from 0.2 nM-77 nM[1]. Lorlatinib significantly inhibits cell proliferation and induces cell apoptosis in the HCC78 human NSCLC cells harboring SLC34A2-ROS1 fusions and the BaF3-CD74-ROS1 cells expressing human CD74-ROS1. Lorlatinib also shows potent growth inhibitory activity and induces apoptosis in the NSCLC cells harboring either non-mutant ALK or mutant ALK fusions[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In rats, Lorlatinib (PF-06463922) displays low plasma clearance, a moderate volume of distribution, a reasonable half-life, low propensity for p-glycoprotein 1-mediated efflux and a bioavailability of 100%[1]. In vivo, Lorlatinib shows cytoreductive antitumor efficacy in the NIH3T3 xenograft models expressing human CD74-ROS1 and Fig-ROS1 via inhibition in ROS1 phosphorylation and the downstream signaling molecules, as well as inhibition of the cell cycle protein Cyclin D1 in tumors. Lorlatinib also demonstrates marked antitumor activity in mice bearing tumor xenografts expressing EML4-ALK, EML4-ALK-L1196M, EML4-ALK-G1269A, EML4-ALK-G1202R or NPM-ALK[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Cells are seeded in 96-well plates in growth medium containing 10% FBS and are cultured overnight at 37°C. The following day, serial dilutions of Lorlatinib or appropriate controls are added to the designated wells, and cells are incubated at 37°C for 72 h. A CellTiter-Glo assay is performed to determine the relative cell numbers. IC_{50} values are calculated by concentration-response curve fitting using a four-parameter analytical method. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	De novoGBM tumorigenesis is initiated in LSL-FIG-ROS1;Cdkn2a−/−;LSL-Luc mice through intracranial stereotactic injections of Adeno-Cre as described previously. Tumor development is monitored using BLI as described below. Once tumors reach a given size (10^7 $p^{-1}{\cdot}s^{-1}{\cdot}cm^{-2}{\cdot}sr^{-1}$), animals are randomLy enrolled into vehicle control or 3-, 7-, or 14-d treatment with the indicated doses of Lorlatinib. Drug is administered through s.c. implanted Alzet osmotic pumps. After treatment, mice are killed, GBM tumors are microdissected, and tissues are flash-frozen in liquid N_2. The remaining brains are processed for histology. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Commun. 2017 Oct 30;8(1):1197.
- EMBO Mol Med. 2020 Jul 7;12(7):e11099.
- Cancer Med. 2020 Jun;9(12):4350-4359.
- J Pharmaceut Biomed. 2020, 113733.
- Fundam Clin Pharmacol. 2021 Feb 1.

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REFERENCES

[1]. Johnson TW, et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical

brain exposure and broad-spectrum potency against ALK-resistant mutations. J Med Chem. 2014 Jun 12;57(11):4720-44.

[2]. Zou HY, et al. PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking PF-02341066-resistant ROS1 mutations. Proc Natl Acad Sci U S A. 2015 Mar 17;112(11):3493-8

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