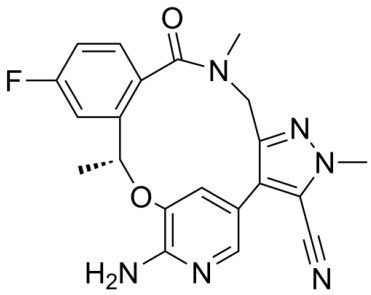
Data Sheet

Product Name:	Lorlatinib
Cat. No.:	CS-3983
CAS No.:	1454846-35-5
Molecular Formula:	$C_{21}H_{19}FN_6O_2$
Molecular Weight:	406.41
Target:	Anaplastic lymphoma kinase (ALK); Apoptosis; ROS Kinase
Pathway:	Apoptosis; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 28 mg/mL



BIOLOGICAL ACTIVITY:

Lorlatinib (PF-06463922) is a selective, orally active, brain-penetrant and ATP-competitive **ROS1/ALK** inhibitor. Lorlatinib has **K_i**s 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]. IC50 & 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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

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. **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.

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

[3]. Zou HY, et al. PF-06463922, an ALK/ROS1 Inhibitor, Overcomes Resistance to First and Second Generation ALK Inhibitors in Preclinical Models. Cancer Cell. 2015 Jul 13;28(1):70-81.

CAIndexNames:

2H-4,8-Methenopyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile, 7-amino-12-fluoro-10,15,16,17-tetrahydro-2,10,16-trimethyl-15-oxo-, (10R)-

SMILES:

CN1C(C#N)=C2C(CN(C)C(C3=C([C@@H](C)OC4=C(N)N=CC2=C4)C=C(F)C=C3)=O)=N1

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