

Product Data Sheet

Product Name: PF-06463922

Cat. No.: GC14794

Chemical Properties

Cas. No. 1454846-35-5

SMILES FC1=CC([C@H](OC2=C(N)N=CC(C3=C(C#N)N(C)N=C3CN4C)=C2)C)=C(C4=O)C=C1

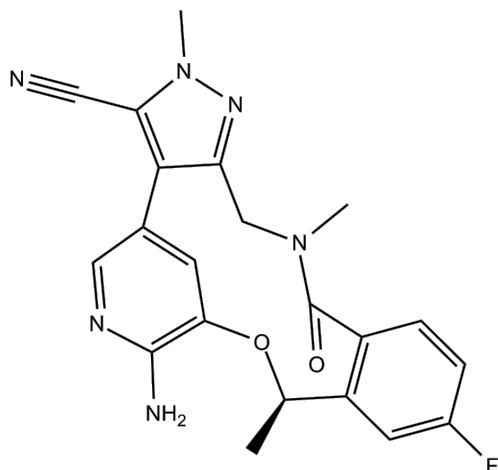
Formula $C_{21}H_{19}FN_6O_2$ M.Wt 406.41

Solubility $\geq 20.3\text{mg/mL}$ 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

Cell experiment [1]:

Cell lines H3122 and H2228 cells (ALK-positive non-small cell lung cancer cell lines)

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Preparation Method H3122 and H2228 cells were cultured in RPMI-1640 supplemented with 10% FBS. The cells were treated with PF-06463922 at 10nM for 24-48 hours.

Reaction Conditions 10nM; 24-48h.

Applications PF-06463922 effectively inhibited the proliferation and induced apoptosis in ALK-positive NSCLC cells. PF-06463922 activated protective autophagy, which could gradually lead to decreased cytotoxicity. However, when combined with the autophagy inhibitor chloroquine (CQ), PF-06463922-induced autophagy was inhibited, and apoptosis was significantly enhanced via activation of the Foxo3a/Bim axis.

Animal experiment [2]:

Animal models Sexually mature male C57BL/6N mice

Preparation Method Ten-week-old male mice were treated orally with PF-06463922 (10mg/kg) for 3 weeks. Some mice were euthanized for analysis immediately after the treatment, while others were allowed a 3-week recovery period after drug discontinuation before analysis.

Dosage form 10mg/kg; p.o.; daily for 3 weeks.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Applications

PF-06463922 administration for 3 weeks reversibly suppressed male fertility. PF-06463922 impaired the maintenance of the epididymal initial segment epithelium, decreased the levels of epididymal proteins (OVCH2, RNASE10, ADAM28), and led to abnormal processing of the sperm membrane protein ADAM3. Consequently, sperm from treated mice lost their ability to bind to the zona pellucida, and sperm motility was significantly impaired. All these effects, including fertility, recovered 3 weeks after discontinuation of the treatment.

References:

- [1] Lu C, Yu R, Zhang C, et al. Protective autophagy decreases lorlatinib cytotoxicity through Foxo3a-dependent inhibition of apoptosis in NSCLC. *Cell Death Discov.* 2022 Apr 22;8(1):221.
- [2] Oyama Y, Shimada K, Miyata H, et al. Inhibition of ROS1 activity with lorlatinib reversibly suppresses fertility in male mice. *Andrology.* 2025 Oct;13(7):1891-1900.

Background

PF-06463922 is a novel, orally active dual inhibitor of ALK (IC₅₀=15-113nM) and ROS1 (K_is=0.025-0.7nM)^[1-2]. PF-06463922 blocks downstream signaling pathways by inhibiting the phosphorylation of ALK and ROS1 kinases. PF-06463922 is used in the treatment of locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC)^[3-4].

In vitro, PF-06463922 (0.01-1μM) was used to treat ALK-rearranged non-small cell lung cancer cell lines (such as H3122 and H2228) for 16-96 hours. PF-06463922 significantly induced BIM expression and promoted apoptosis, while simultaneously downregulating NOXA, leading to MCL-1-dependent anti-apoptotic adaptation^[5]. PF-06463922 (10nM) treated ALK-positive NSCLC cells (H3122 and H2228 cell lines) for 24-48 hours. PF-06463922 effectively inhibited cell proliferation and induced apoptosis, while also triggering protective autophagy^[6].

In vivo, PF-06463922 (5mg/kg; p.o.; daily for 14days) was used to treat C57BL/6 mice bearing orthotopic pancreatic ductal adenocarcinoma (PDAC) or colorectal cancer (CRC) liver metastasis models. PF-06463922 significantly reduced the weight of primary tumors and metastases, decreased intratumoral neutrophil accumulation and fibrosis, and inhibited tumor cell proliferation^[7]. PF-

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

06463922 (orally administered at 10mg/kg daily for 3 weeks) was used to treat 10-week-old sexually mature male C57BL/6N mice. PF-06463922 reversibly suppressed male fertility, impaired sperm's ability to bind to the zona pellucida, led to abnormal processing of ADAM3, and compromised sperm motility^[8].

References:

- [1] Johnson TW, Richardson PF, Bailey S, 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, Friboulet L, Kodack DP, 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.
- [3] Solomon BJ, Liu G, Felip E, et al. Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. *J Clin Oncol*. 2024 Oct 10;42(29):3400-3409.
- [4] Shaw AT, Bauer TM, de Marinis F, et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. *N Engl J Med*. 2020 Nov 19;383(21):2018-2029.
- [5] Martín F, Alcon C, Marín E, Morales-Sánchez P, et al. Novel selective strategies targeting the BCL-2 family to enhance clinical efficacy in ALK-rearranged non-small cell lung cancer. *Cell Death Dis*. 2025 Mar 20;16(1):194.
- [6] Lu C, Yu R, Zhang C, et al. Protective autophagy decreases lorlatinib cytotoxicity through Foxo3a-dependent inhibition of apoptosis in NSCLC. *Cell Death Discov*. 2022 Apr 22;8(1):221.
- [7] Nielsen SR, Strøbech JE, Horton ER, et al. Suppression of tumor-associated neutrophils by lorlatinib attenuates pancreatic cancer growth and improves treatment with immune checkpoint blockade. *Nat Commun*. 2021 Jun 7;12(1):3414.
- [8] Oyama Y, Shimada K, Miyata H, et al. Inhibition of ROS1 activity with lorlatinib reversibly suppresses fertility in male mice. *Andrology*. 2025 Oct;13(7):1891-1900.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA