Selitrectinib

Cat. No.: HY-101977

CAS No.: 2097002-61-2

Molecular Formula: $C_{20}H_{21}FN_6O$

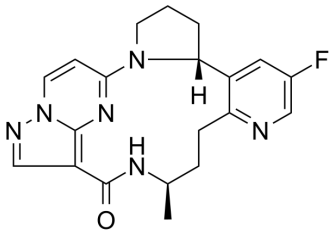
Molecular Weight: 380.42

Target: Trk Receptor

Pathway: Neuronal Signaling; Protein Tyrosine Kinase/RTK

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : 62.5 mg/mL (164.29 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6287 mL	13.1434 mL	26.2867 mL
	5 mM	0.5257 mL	2.6287 mL	5.2573 mL
	10 mM	0.2629 mL	1.3143 mL	2.6287 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: ≥ 2.08 mg/mL (5.47 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (5.47 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.47 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Selitrectinib (LOXO-195) is a next-generation TRK kinase inhibitor, with IC_{50}s of 0.6 nM and <2.5 nM for TRKA and TRKC, respectively[1].

IC_{50} & Target

TrkA	TrkC
0.6 nM (IC_{50})	<2.5 nM (IC_{50})

In Vitro

Selitrectinib (LOXO-195) demonstrates strong binding to the wild-type TRKA, TRKB and TRKC kinase domains. Selitrectinib

	(LOXO-195) has potent (IC_{50}<1 nM) inhibitory activity in kinase enzyme assays. Importantly, Selitrectinib (LOXO-195) achieves low nanomolar inhibitory activity against TRKA G595R, TRKC G623R, and TRKA G667C, with IC_{50}s ranging from 2.0-9.8 nM. 228 individual kinases in vitro are profiled at a Selitrectinib (LOXO-195) concentration of 1 μM, which is ~1667-fold higher than its IC_{50} for TRKA (0.6 nM). Selitrectinib (LOXO-195) is more than 1000-fold selective for 98% of non-TRK kinases tested. Selitrectinib (LOXO-195) demonstrates potent inhibition of cell proliferation in TRK fusion-containing KM12, CUTO-3, and MO-91 cell lines (IC_{50}≤5 nM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Stably transfected NIH-3T3 ΔTRKA and ΔTRKA-G595R cells are implanted subcutaneously into the flanks of nude mice. Both larotrectinib and Selitrectinib (LOXO-195) are effective at reducing phosphorylated TRKA in tumors driven by ΔTRKA. In contrast, only Selitrectinib (LOXO-195) strongly suppresses phospho-TRKA in ΔTRKA-G595R cells in a dose-dependent manner. Selitrectinib (LOXO-195) also causes inhibition of tumor growth relative to vehicle at all doses in four TRKA-dependent tumor models (ΔTRKA, ΔTRKA-G595R, ΔTRKAG667C, and TPM3-NTRK1 fusion-positive KM12 colorectal cancer cells. Larotrectinib inhibits KM12 and NIH 3T3-ΔTRKA tumors to a similar degree. Group mean body weight loss does not exceed 5% for any agent. Selitrectinib (LOXO-195) displays high selectivity for the TRK proteins[1] MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	For assessment of cellular inhibition potency, cells are harvested per a standard protocol, counted and added to flat-bottom, collagen I-coated 96-well assay plates at 3×10^4 cells/well (wild-type cell line) or 5×10^4 cells/well (mutant cell lines) in 100 μL/well of DMEM growth medium containing 10% FBS. Plates are then incubated at room temperature for 30 minutes prior to an overnight incubation at 37°C with 5% CO_2. Next, cells are treated for 1 hour at 37°C, 5% CO_2 with TRK inhibitor compounds (e.g., Selitrectinib (LOXO-195)). Control wells contain either 0.25% DMSO alone or 1 μM larotrectinib or LOXO-195. Following compound incubation, growth medium is discarded and cells are lysed by addition of 60 μL/well of ice-cold lysis buffer containing protease and phosphatase inhibitors[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] The ΔTRKA, ΔTRKA-G595R, and ΔTRKA -G667C NIH-3T3 tumor cell lines (~2-3x10^6 cells) and KM12 cells (5x10^6 cells) are injected subcutaneously into the right flank of female nu/nu NCr mice. Tumors are allowed to grow to ~100-200 mm^3 or ~500 mm^3, and animals are randomized by tumor size into dosing groups of 5 (KM12), 7 (NIH 3T3 ΔTRKA variants) or 3-4 (for PK-PD) animals. Animals are dosed by oral gavage with vehicle, Selitrectinib (LOXO-195) in 1% carboxymethylcellulose/0.5% Tween-80 or larotrectinib in 100% Labrafac lipophile. All animals are obtained at 6-8 weeks of age, housed in groups of 5 and allowed a one-week acclimation period before cancer cell injection. Animals are dosed with vehicle twice daily, Selitrectinib (LOXO-195) at 30 mg/kg, 100 mg/kg and 300 mg/kg twice daily and larotrectinib at 60 mg/kg daily for 9-12 days. Body weight and tumor size are monitored after cell implantation and at regular intervals during dosing[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Mol Cancer Ther. 2021 Oct 8;molcanther.MCT-21-0632-A.2021.
- Cancers (Basel). 2023 Aug 24, 15(17), 4246.
- University of Zürich. Department of Dermatology. 2021 Dec.

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REFERENCES

[1]. Drilon A, et al. A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion-Positive Solid Tumors. Cancer Discov. 2017 Sep;7(9):963-972.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA