Larotrectinib sulfate

Cat. No.: HY-12866A

CAS No.: 1223405-08-0

Molecular Formula: $C_{21}H_{24}F_2N_6O_6S$

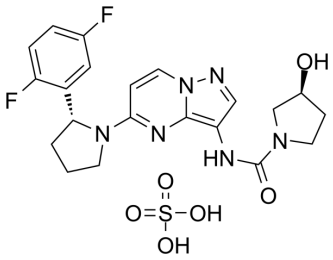
Molecular Weight: 526.51

Target: Trk Receptor; Apoptosis

Pathway: Neuronal Signaling; Protein Tyrosine Kinase/RTK; Apoptosis

Storage: 4°C, sealed storage, away from moisture

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (94.96 mM; Need ultrasonic)

H_2O : 2 mg/mL (3.80 mM; ultrasonic and adjust pH to 2 with 1M HCl)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8993 mL	9.4965 mL	18.9930 mL
5 mM	0.3799 mL	1.8993 mL	3.7986 mL
10 mM	0.1899 mL	0.9496 mL	1.8993 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: PBS
   Solubility: 12.5 mg/mL (23.74 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 3.25 mg/mL (6.17 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 3.25 mg/mL (6.17 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3.25 mg/mL (6.17 mM); Clear solution
5. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (4.75 mM); Clear solution
6. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.75 mM); Clear solution

BIOLOGICAL ACTIVITY

Description Larotrectinib sulfate (LOXO-101 sulfate; ARRY-470 sulfate) is an ATP-competitive oral, selective inhibitor of the tropomyosin-

	related kinase (TRK) family receptors, with low nanomolar 50% inhibitory concentrations against all three isoforms (TRKA, B, and C).		
IC_{50} & Target	TrkA	TrkB	TrkC
In Vitro	Larotrectinib (LOXO-101) is an ATP-competitive oral inhibitor of the tropomyosin-related kinase (TRK) family of receptor kinases (TRKA, B, and C), with low nanomolar 50% inhibitory concentrations against all three isoforms, and 1,000-fold or greater selectivity relative to other kinases[1][2]. Measurement of proliferation following treatment with Larotrectinib (LOXO-101) demonstrates a dose-dependent inhibition of cell proliferation in all three cell lines. The IC_{50} is less than 100 nM for CUTO-3.29 and less than 10 nM for KM12 and MO-91 consistent with the known potency of this drug for the TRK kinase family [3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.		
In Vivo	In rat and monkey studies, Larotrectinib (LOXO-101) demonstrates 33-100% oral bioavailability and 60-65% plasma protein binding. It has low brain penetration, and is well tolerated in 28 day (d) GLP toxicology studies. A single dose (30 mg/kg) of Larotrectinib (LOXO-101) reduces tyrosine phosphorylation of TRKA and downstream signal transduction (pERK) in the tumor >80%[1]. Athymic nude mice injected with KM12 cells are treated with Larotrectinib sulfate orally daily for 2 weeks. Dose-dependent tumor inhibition is observed demonstrating the ability of this selective compound to inhibit tumor growth in vivo[4]. Larotrectinib (LOXO-101) (200mg/kg/day p.o for six weeks) reduces leukemic infiltration to undetectable levels in the bone marrow and spleen compared to vehicle-treated mice. Mice treated with Larotrectinib sulfate are still alive and leukemia-free four weeks after the cessation of treatment, as determined by Xenogen imaging[5]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.		

PROTOCOL

Animal Administration [4]	Mice[4] Athymic nude mice are used throughout the study. 5×10^5 KM12 cells are injected subcutaneously into the dorsal flank area of the mice. Tumor volume is monitored by direct measurement with calipers and calculated by the formula: length × (width ^{2})/2. Following the establishment of tumor and when the tumor size is between 150-200 mm^2, mice are randomly selected to receive diluent, 60 mg/kg/dose or 200 mg/kg/dose of Larotrectinib (LOXO-101). Larotrectinib (LOXO-101) is administered by oral gavage once daily for 14 days. After the last dose, tissue and blood are collected at 3, 6 and 24 hours post-treatment [4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Rep Med. 2023 Jan 10;100911.
- Eur J Med Chem. 2020 Aug 30;207:112744.
- Mol Oncol. 2022 Oct 1.
- Mol Cancer Ther. 2021 Oct 8;molcanther.MCT-21-0632-A.2021.
- Spectrochim Acta A Mol Biomol Spectrosc. 2023 Nov 5, 300, 122914.

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REFERENCES

[1]. Doebele RC, et al. An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101. Cancer

Discov. 2015 Oct;5(10):1049-57.

[2]. Karyn Bouhana, et al. LOXO-101, a pan TRK inhibitor, For The Treatment Of TRK-driven Cancers.

[3]. Nagasubramanian R, et al. Infantile Fibrosarcoma With NTRK3-ETV6 Fusion Successfully Treated With the Tropomyosin-Related Kinase Inhibitor LOXO-101. Pediatr Blood Cancer. 2016 Aug;63(8):1468-70.

[4]. Kathryn G, et al. Genetic Modeling and Therapeutic Targeting of ETV6-NTRK3 with Loxo-101in Acute Lymphoblastic Leukemia. Blood 2016 128:278.

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