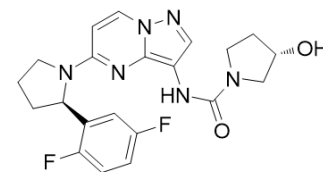


LOXO-101

Cat. No.:	HY-12866		
CAS No.:	1223403-58-4		
Molecular Formula:	C ₂₁ H ₂₂ F ₂ N ₆ O ₂		
Molecular Weight:	428.44		
Target:	Trk Receptor		
Pathway:	Protein Tyrosine Kinase/RTK		
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 : ≥ 4.6 mg/mL (10.74 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent	Mass	1 mg	5 mg	10 mg
	Concentration				
	1 mM		2.3340 mL	11.6702 mL	23.3405 mL
	5 mM		0.4668 mL	2.3340 mL	4.6681 mL
	10 mM		0.2334 mL	1.1670 mL	2.3340 mL

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

BIOLOGICAL ACTIVITY

Description

LOXO-101 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).

IC₅₀ & Target

TrkA	TrkB	TrkC
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In Vitro

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 LOXO-101 demonstrates a dose-dependent inhibition of cell proliferation in all three cell lines. The IC₅₀ 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].

In Vivo

In rat and monkey studies, 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 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 LOXO-101 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]. 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 LOXO-101 are still alive and leukemia-free four weeks after the cessation of treatment, as determined by Xenogen imaging [5].

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 \times (width²)/2. Following the establishment of tumor and when the tumor size is between 150-200 mm², mice are randomly selected to receive diluent, **60 mg/kg/dose** or **200 mg/kg/dose** of **LOXO-101**. 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.

REFERENCES

- [1]. Karyn Bouhana, et al. LOXO-101, a pan TRK inhibitor, For The Treatment Of TRK-driven Cancers.
- [2]. 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.
- [3]. 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.
- [4]. 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.
- [5]. Kathryn G, et al. Genetic Modeling and Therapeutic Targeting of ETV6-NTRK3 with Loxo-101 in Acute Lymphoblastic Leukemia. *Blood* 2016 128:278.

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

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