Taletrectinib

Cat. No.: HY-131003

CAS No.: 1505515-69-4

Molecular Formula: $C_{29}H_{34}FN_5O_5$

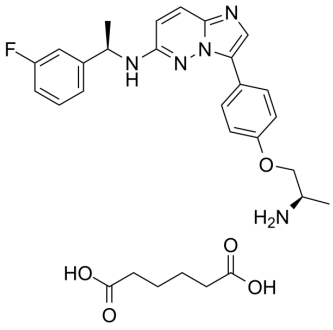
Molecular Weight: 552

Target: ROS Kinase

Pathway: Protein Tyrosine Kinase/RTK

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 (90.58 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8116 mL	9.0580 mL	18.1159 mL
	5 mM	0.3623 mL	1.8116 mL	3.6232 mL
	10 mM	0.1812 mL	0.9058 mL	1.8116 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 (3.77 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (3.77 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.77 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Taletrectinib (DS-6051b) is a potent, orally active, and next-generation selective ROS1/NTRK inhibitor. Taletrectinib potently inhibits recombinant ROS1, NTRK1, NTRK2, and NTRK3 with IC_{50}s of 0.207, 0.622, 2.28, and 0.98 nM, respectively. Taletrectinib also inhibits ROS1 G2032R and other Crizotinib-resistant ROS1 mutants[1][2].

In Vitro

The IC_{50} of Taletrectinib (1-1000 nM; 72 hours) against Ba/F3-TPM3-NTRK1, Ba/F3-ETV6-NTRK1, -NTRK2, -NTRK3, or KM12 cells is ~3-20 nM[1].

Taletrectinib (0.001-1000 nM; 2 hours) dose dependently inhibited autophosphorylation of ROS1 in U-118-MG cells in vitro[1].

Taletrectinib potently inhibits autophosphorylation of ROS1 in JFCR-165, JFCR-168, and MGH193-1B cells[1].

Taletrectinib partially suppresses phospho-NTRK1 at 10 nM, and completely suppresses by 100 nM. Taletrectinib free base

potently inhibits recombinant ROS1, NTRK1, and NTRK3 in sub-nanomolar concentration in an ATP-competitive manner.
Taletrectinib almost completely inhibits ACK, ALK, DDR1, and LTK at 0.2 μM among 160 kinases in the presence of 1 mM ATP, but did not inhibit other 152 kinases strongly[1].
Taletrectinib effectively inhibits Crizotinib-resistant ROS1 secondary mutations, including G2032R solvent front mutation[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	TPM3-NTRK1-induced Ba/F3 cells, KM12 cells
Concentration:	1-1000 nM
Incubation Time:	72 hours
Result:	Inhibited TPM3-NTRK1-induced Ba/F3 cells and KM12 cells viability.

Western Blot Analysis[1]

Cell Line:	U-118 MG cells (harboring FIG-ROS1 fusion gene)
Concentration:	0.001-1000 nM
Incubation Time:	2 hours
Result:	Dose dependently inhibited autophosphorylation of ROS1 in U-118-MG cells.

In Vivo

Taletrectinib (DS-6051b) (25-200 mg/kg; p.o.; once daily for 18 days) shows antitumor activity[1].
Taletrectinib (6.25-200 mg/kg; p.o.; once daily for 8 days) inhibits NTRK-rearranged cancer in Balb-c nu/nu mice bearing KM12 cells[1].
Taletrectinib (3-100 mg/kg; p.o.; once daily for 4 days) shows rapid tumor regression in the wild-type (WT) and the G2032R-mutant Ba/F3-bearing mice without severe body weight loss[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Balb-c nu/nu mice (bearing U-118 MG cells)[1]
Dosage:	25, 50, 100, and 200 mg/kg
Administration:	P.o.; once daily for 18 days
Result:	Effectively inhibited tumor growth at ≥25 mg/kg without significant body weight loss.

REFERENCES

[1]. Katayama R, et al. The new-generation selective ROS1/NTRK inhibitor DS-6051b overcomes crizotinib resistant ROS1-G2032R mutation in preclinical models. Nat Commun. 2019;10(1):3604. Published 2019 Aug 9.

[2]. Fujiwara Y, et al. Safety and pharmacokinetics of DS-6051b in Japanese patients with non-small cell lung cancer harboring ROS1 fusions: a phase I study. Oncotarget. 2018;9(34):23729-23737. Published 2018 May 4.

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