Taletrectinib free base

Cat. No.: HY-131003A

CAS No.: 1505514-27-1

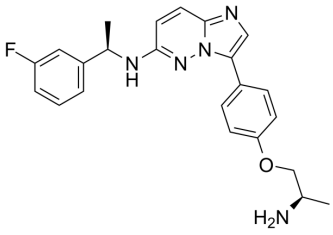
Molecular Formula: $C_{23}H_{24}FN_5O$

Molecular Weight: 405.47

Target: ROS Kinase

Pathway: Protein Tyrosine Kinase/RTK

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

Taletrectinib (DS-6051b) free base is a potent, orally active, and next-generation selective ROS1/NTRK inhibitor. Taletrectinib free base 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 free base also inhibits ROS1 G2032R and other Crizotinib-resistant ROS1 mutants[1][2].

In Vitro

The IC_{50} of Taletrectinib free base (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 free base (0.001-1000 nM; 2 hours) dose dependently inhibited autophosphorylation of ROS1 in U-118-MG cells in vitro[1].

Taletrectinib (DS-6051b) free base potently inhibits autophosphorylation of ROS1 in JFCR-165, JFCR-168, and MGH193-1B cells[1].

Taletrectinib free base 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 free base 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 free base 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) free base (25-200 mg/kg; p.o.; once daily for 18 days) shows antitumor activity[1].
Taletrectinib free base (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 free base (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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