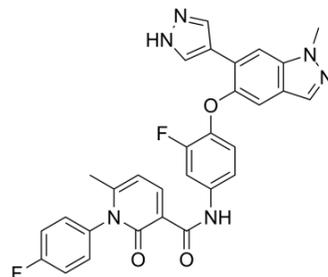


Merestinib

Cat. No.:	HY-15514		
CAS No.:	1206799-15-6		
Molecular Formula:	C ₃₀ H ₂₂ F ₂ N ₆ O ₃		
Molecular Weight:	552.53		
Target:	c-Met/HGFR; FLT3; ROS; Discoidin Domain 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 : ≥ 32 mg/mL (57.92 mM)
 * "≥" means soluble, but saturation unknown.

Concentration	Mass		
	1 mg	5 mg	10 mg
1 mM	1.8099 mL	9.0493 mL	18.0986 mL
5 mM	0.3620 mL	1.8099 mL	3.6197 mL
10 mM	0.1810 mL	0.9049 mL	1.8099 mL

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

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
 Solubility: ≥ 2.08 mg/mL (3.76 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
 Solubility: ≥ 2.08 mg/mL (3.76 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
 Solubility: ≥ 2.08 mg/mL (3.76 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Merestinib (LY2801653) is a potent, orally bioavailable c-Met inhibitor ($K_i=2$ nM) with anti-tumor activities. Merestinib (LY2801653) also has potent activity against MST1R ($IC_{50}=11$ nM), FLT3 ($IC_{50}=7$ nM), AXL ($IC_{50}=2$ nM), MERTK ($IC_{50}=10$ nM), TEK ($IC_{50}=63$ nM), ROS1, DDR1/2 ($IC_{50}=0.1/7$ nM) and MKNK1/2 ($IC_{50}=7$ nM)^{[1][2]}.

IC₅₀ & Target

Ki: 2 nM (c-Met)^[1]
 IC₅₀: 11 nM (MST1R), 7 nM (FLT3), 2 nM (AXL), 10 nM (MERTK), 63 nM (TEK), 0.1/7 nM (DDR1/2), 7 nM (MKNK1/2)^[1]

In Vitro	<p>Merestinib (LY2801653) demonstrates effects on MET pathway-dependent cell scattering and cell proliferation. The mean IC₅₀ value (n=6 determinations) of Merestinib (LY2801653) for inhibition of MET auto-phosphorylation in HGF-stimulated H460 cells is 35.2±6.9 nM and the IC₅₀ for MET auto-phosphorylation in S114 cells is 59.2 nM. Merestinib (LY2801653) also inhibits MST1R (IC₅₀=11 nM), AXL (IC₅₀=2 nM), MERTK (IC₅₀=10 nM), TYRO3 (IC₅₀=28 nM), ROS1, PDGFRA (IC₅₀=41 nM), FLT3 (IC₅₀=7 nM), TEK (IC₅₀=63 nM), DDR1/2 (IC₅₀=0.1/7 nM) and MKNK1/2 (IC₅₀=7 nM)^[1].</p> <p>Transfection with the MET variants confers growth-factor independence and treatment with Merestinib (LY2801653) inhibits growth of these MET variant clones with an IC₅₀ ranging from 3-fold more potent (V1092I) to approximately 6-fold less potent (L1195V) compare with the growth inhibition of cells with the MET wild-type sequence^[1]. Merestinib (LY2801653) (2, 5, and 10 μM) reduces the number of viable TFK-1 and SZ-1 cells in a dose and time dependent manner, and significant inhibits wound healing for TFK-1 and SZ-1 cell lines. Merestinib (LY2801653) inhibits cell invasion in TFK-1 and SZ-1 cells in a concentration dependent manner^[2].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
In Vivo	<p>Merestinib (LY2801653) demonstrates anti-tumor effects in MET amplified (MKN45), MET autocrine (U-87MG, and KP4) and MET over-expressed (H441) xenograft models; and in vivo vessel normalization effects. Merestinib (LY2801653) is a type-II ATP competitive, slow-off inhibitor of MET tyrosine kinase with a pharmacodynamic residence time (K_{off}) of 0.00132 min⁻¹ and t_{1/2} of 525 min. Merestinib (LY2801653) treatment inhibits MET phosphorylation with a composite TED50 (50 % target inhibition dose) of 1.2 mg/kg and a composite TED90 (90 % target inhibition dose) of 7.4 mg/kg^[1]. Merestinib (LY2801653) (20 mg/kg) reduces TFK-1 tumor growth significantly relative to vehicle control. Merestinib (LY2801653) inhibits the growth of intra- and extrahepatic CCC xenograft tumors^[2].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

PROTOCOL

Cell Assay ^[1]	<p>H460 cells are cultured in RPMI media supplemented with 10% FBS and plated (prior to becoming 70% confluent) in 96-well plates at 20,000 cells/well and are incubated overnight at 37°C. The next day, the cells are incubated with RPMI-1640 in low serum (0.5% FBS) for 2 hours prior to treatment with Merestinib (LY2801653). Thirty minutes after the addition of Merestinib (LY2801653), HGF at a final concentration of 100ng/mL is added. After a 10-minute incubation, cell lysates are prepared and pMET is quantified. Relative IC₅₀ values are determined using MSD activity units by calculating the percentage of inhibition with respect to on-plate MIN (unstimulated) and MAX controls and then fitting the percentage-of-inhibition values and 10-point dose response data to a 4-parameter logistic equation using ActivityBase^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Animal Administration ^[1]	<p>Mice^[1]</p> <p>S114 cells are implanted subcutaneously onto female athymic nude mice. For dose response evaluation, on day 8 after the implantation, Merestinib is given at a range of 0.75 mg/kg to 100 mg/kg (n=8 per dose group). At 2 hours after dose, blood samples and tumors are collected and flash frozen. For time course study, Merestinib is given at 12 mg/kg (n=10 per time point). Animals are sacrificed at 2, 8, 16, and 24 hours after dose, and blood samples and tumors are collected. pMET is measured in the S114 tumor lysates using the MSD ELISA assay. Lysates are prepared from pulverized frozen tumor tissue, and homogenized with Lysing Matrix D beads, with addition of RIPA lysis buffer containing phosphatase and protease inhibitors. Protein concentration is determined using the DC protein assay kit. The pMET MSD ELISA assay is performed.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

CUSTOMER VALIDATION

- Cancer Discov. 2016 Dec;6(12):1334-1341.
- Clin Cancer Res. 2020 Jun 1;26(11):2615-2625.
- Methods Mol Biol. 2018;1711:351-398.

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- Patent. WO2017019702A1.

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REFERENCES

[1]. Yan SB, et al. LY2801653 is an orally bioavailable multi-kinase inhibitor with potent activity against MET, MST1R, and other oncoproteins, and displays anti-tumor activities in mouse xenograft models. Invest New Drugs. 2013 Aug;31(4):833-44.

[2]. Barat S, et al. Targeting c-MET by LY2801653 for treatment of cholangiocarcinoma. Mol Carcinog. 2016 Jan 12.

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

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