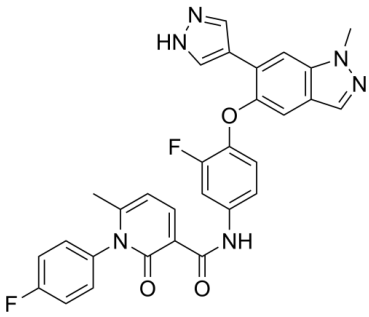
Data Sheet

Product Name:	Merestinib
Cat. No.:	CS-1192
CAS No.:	1206799-15-6
Molecular Formula:	$C_{30}H_{22}F_2N_6O_3$
Molecular Weight:	552.53
Target:	c-Met/HGFR; Discoidin Domain Receptor; FLT3; ROS Kinase
Pathway:	Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 32 mg/mL



BIOLOGICAL ACTIVITY:

Merestinib (LY2801653) is a potent, orally bioavailable **c-Met** inhibitor ($\mathbf{K_i}$=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:*** Merestinib (LY2801653) demonstrates effects on MET pathway-dependent cell scattering and cell proliferation. The mean IC_{50} 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 IC_{50} for MET auto-phosphorylation in S114 cells is 59.2 nM. Merestinib (LY2801653) also inhibits MST1R (IC_{50}=11 nM), AXL (IC_{50}=2 nM), MERTK (IC_{50}=10 nM), TYRO3 (IC50=28 nM), ROS1, PDGFRA (IC50=41 nM), FLT3 (IC_{50}=7 nM), TEK (IC50=63 nM), DDR1/2 (IC_{50}=0.1/7 nM) and MKNK1/2 (IC_{50}=7 nM)[1].
Transfection with the MET variants confers growth-factor independence and treatment with Merestinib (LY2801653) inhibits growth of these MET variant clones with an IC_{50} 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]. ***In Vivo:*** 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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: Merestinib (LY2801653) is prepared in DMSO (10 mM) and stored, and then is diluted serially 1:3 to create a 10-point concentration-response curve (concentration range 20 μM to 0.001 μM in 2% DMSO/reduced serum media). Final assay DMSO concentration (prestimulation) is 0.4%[1].[1]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 IC_{50} 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]. **Animal Administration:** Merestinib (LY2801653) is formulated in 10 % acacia[1].[1]Mice[1]
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.

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.

CAIndexNames:

3-Pyridinecarboxamide, N-[3-fluoro-4-[[1-methyl-6-(1H-pyrazol-4-yl)-1H-indazol-5-yl]oxy]phenyl]-1-(4-fluorophenyl)-1,2-dihydro-6-methyl-2-oxo-

SMILES:

O=C(C1=CC=C(C)N(C2=CC=C(F)C=C2)C1=O)NC3=CC=C(OC4=CC5=C(N(C)N=C5)C=C4C6=CNN=C6)C(F)=C3

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