Product Data Sheet

Product Name: TAS-115
Cat. No.: GC33173

Chemical Properties

Cas. No.	1190836-34-0		
SMILES	O=C(C1=C(OC)C=C2N=CC=C(OC3=CC=C(NC(NC(CC4=CC=CC=C4)=O)=S)C=C3F)C2=C1)NC		
Formula	$C_{27}H_{23}FN_4O_4S$	M.Wt	518.56
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	TAS-115		

Protocol

Kinase experiment:

Enzyme inhibition studies are performed using a mobility shift assay. Briefly, 0.3 μg/mL of recombinant MET (rMET, N-terminal glutathione S-transferase (GST) Tag) and 1.5 μM of FL-Peptide 2 or 2 μg/mL of recombinant VEGFR2 (rVEGFR2, amino acid 790-end, N-terminal 6His Tagged) and 1.5 μM of FL-Peptide 22 are added to a 25 μL mixture containing 1/2 the Michaelis constant (Km) level of ATP, 100 mM of HEPES (pH 7.2), 0.003% (w/v) Brij35, 0.04% (v/v) Tween 20, 10 mM of MgCl2, 1 mM of dithiothreitol, a Complete Mini EDTA-free Protease Inhibitor Cocktail Tablet, and a PhosSTOP Phosphatase Inhibitor Cocktail Tablet, with the addition of 0.05% (w/v) CHAPSO only in the case of rVEGFR2. The reaction mixture is incubated for 90 minutes at 28°C and is stopped by the addition of 15 mM of EDTA. Phosphorylated peptide is calculated using a LabChip EZ Reader, Version 2.1.82.0 (UCC Version: 1.96, CCD Version: 102). On the basis of the amount of phosphorylated peptide formed in the control well and the drug-treated well, the 50% inhibitory concentration (IC50) is calculated using a logistic regression analysis. A total of 192 kinase panel assays is performed using the ProfilerPro Kit 1-8 and is analyzed using a mobility shift assay.

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Cell experiment:	Cell growth is measured using the MTT dye reduction method. Tumor cells are plated into 96-well plates at a density of 2×103 cells/100 mL RPMI-1640 medium with 10% FBS per well. After 24-hour incubation, various reagents are added to each well, and the cells incubated for a further 72 hours, followed by the addition of 50 μL of MTT solution (2 mg/mL) to each well and incubation for 2 hours. The media containing MTT solution is removed, and the dark blue crystals are dissolved by adding 100 mL of dimethyl sulfoxide. The absorbance of each well is measured with a microplate reader at test and reference wavelengths of 550 and 630 nm, respectively. The percentage of growth is shown relative to untreated controls. Each reagent concentration is tested at least in triplicate during each experiment, and each experiment is conducted at least three times.
Animal experiment:	A SC-9 fragment is implanted subcutaneously into the right abdomen of each mouse via a trocar. Suspensions of MKN45 cells are prepared and are implanted subcutaneously into the right abdomen of each nude mouse. The tumor volume (TV, mm3) is calculated. The TAS-115 dose levels are set at 12.5, 50, and 200 mg/kg/d. The dose level for sunitinib is set at 40 mg/kg/d; this dose is equivalent to the maximum tolerated dose (MTD). Oral drug treatment is continued for 14 or 42 consecutive days for the chronic dosing in the SC-9 xenograft model. During the treatment period, TV and body weight are measured twice per week.

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References:

[1]. Fujita H, et al. The novel VEGF receptor/MET-targeted kinase inhibitor TAS-115 has marked in vivo antitumor properties and a favorable tolerability profile. Mol Cancer Ther. 2013 Dec;12(12):2685-96.
[2]. Nakade J, et al. Triple inhibition of EGFR, Met, and VEGF suppresses regrowth of HGF-triggered, erlotinib-resistant lung cancer harboring an EGFR mutation. J Thorac Oncol. 2014 Jun;9(6):775-83.

Background

TAS 115 is a multi-kinase inhibitor that inhibits the growth factor receptors PDGFRα and PDGFRβ (IC_{50}s = 0.81 and 7.06 nM, respectively), c-FMS (IC_{50} = 15 nM), VEGFR2 and VEGFR1 (IC_{50}s = 30 and 140 nM, respectively), Met (IC_{50} = 32 nM), and FGFR2 (IC_{50} = 340 nM).[1,2] It also inhibits Axl, c-Kit, Src, and FLT1.[1] TAS 115 inhibits VEGF-induced VEGFR2 phosphorylation in human umbilical vein endothelial cells (HUVECs) and Met phosphorylation in Met-amplified MKN45 human gastric cancer cells. It also inhibits

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VEGF-dependent, but not VEGF-independent, growth of HUVECs (IC_{50}s = 0.019 and 19.3 ?M, respectively) and of Met-amplified MKN45, but not Met-inactivated, human MCF-7 breast cancer cells (GI_{50}s = 0.032 and >10 ?M, respectively). TAS 115 reduces tumor growth in a MKN45 mouse xenograft model (ED_{50} = 8 mg/kg).

1.Fujita, H., Miyadera, K., Kato, M., et al.The novel VEGF receptor/MET-targeted kinase inhibitor TAS-115 has marked in vivo antitumor properties and a favorable tolerability profileMol. Cancer Ther.12(12)2685-2696(2013) 2.Koyama, K., Goto, H., Morizumi, S., et al.The tyrosine kinase inhibitor TAS-115 attenuates bleomycin-induced lung fibrosis in miceAm. J. Respir. Cell Mol. Biol.60(4)478-487(2019)

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