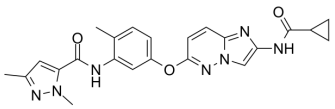
TAK-593

Cat. No.:	HY-15506
CAS No.:	1005780-62-0
Molecular Formula:	$C_{23}H_{23}N_7O_3$
Molecular Weight:	445.47
Target:	PDGFR; VEGFR
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 48.5 mg/mL (108.87 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2448 mL	11.2241 mL	22.4482 mL
5 mM	0.4490 mL	2.2448 mL	4.4896 mL
10 mM	0.2245 mL	1.1224 mL	2.2448 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: ≥ 2.67 mg/mL (5.99 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.67 mg/mL (5.99 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.67 mg/mL (5.99 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

TAK-593 is a potent VEGFR and PDGFR family inhibitor with IC_{50}s of 3.2, 0.95, 1.1, 4.3 and 13 nM for VEGFR1, VEGFR2, VEGFR3, PDFGRα and PDFGRβ, respectively.

IC_{50} & Target

VEGFR1 3.2 nM (IC_{50})	VEGFR2 0.95 nM (IC_{50})	VEGFR3 1.1 nM (IC_{50})	PDGFRα 4.3 nM (IC_{50})
PDGFRβ	PDGFRα^{V561D}		

	13 nM (IC_{50})	1 nM (IC_{50})

In Vitro	TAK-593 inhibits growth of HUVEC with an IC_{50} of 0.30 nM. It shows potent inhibitory activity against VEGFR (VEGFR1-3: IC_{50} =3.2, 0.95, 1.1 nM) and PDGFR (PDGFRα, β: IC_{50}=4.3, 13 nM) families. Against other kinases, the IC_{50} values of TAK-593 are above 100 nM, except for Fms (IC_{50}=10 nM) and Ret (IC_{50}=18 nM) kinases[1]. TAK-593 potently inhibits VEGF- and PDGF-stimulated cellular phosphorylation and proliferation of human umbilical vein endothelial cells and human coronary artery smooth muscle cells. TAK-593 also potently inhibits VEGF-induced tube formation of endothelial cells co-cultured with fibroblasts[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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PROTOCOL

Kinase Assay [1]	Enzyme reactions are performed in 50 mM TrisHCl pH 7.5, 5 mM $MnCl_2$, 5 mM $MgCl_2$, 0.01% Tween-20 and 2 mM DTT, containing 10 μM ATP, 0.1 μg/mL biotinylated polyGluTyr (4:1) and 0.1 nM of VEGFR2. Prior to catalytic initiation with ATP, compound (TAK-593) and enzyme are incubated for 5 min at room temperature (preincubation). The reactions are quenched by the addition of 25 μL of 100 mM EDTA, 10 μg/mL AlphaScreen streptavidine donor beads and 10 μg/mL acceptor beads in 62.5 mM HEPES pH 7.4, 250 mM NaCl, and 0.1% BSA. Plates are incubated in the dark overnight and then read by plate reader[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	HUVECs are seeded into a 96-well plate at 3000 cells/well in Human Endothelial-SFM Growth Medium (Invitrogen) containing 3% fetal bovine serum (FBS) and are incubated overnight at 37 C in a 5% CO_2 incubator. Various concentrations of the test compounds (TAK-593) are added in the presence of 60 ng/mL VEGF, and the cells are cultured for a further 5 days. Cellular proliferation is determined by the WST-8 formazan assay using Cell Counting Kit-8[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats: The iv administration in rats is conducted under anesthesia with diethyl ether. At 5, 10 (only for iv dosing), 15, 30 min, and 1, 2, 3, 4, 6, 8, 12, 24, 32 (only for monkeys) and 48 h (only for monkeys) after dosing, blood is taken from the tail vein in rats or from the femoral vein in monkeys. Then, the blood is centrifuged to obtain the plasma fraction. The plasma is kept frozen at 20°C until analysis. The concentration of TAK-593 in plasma is determined by the high-performance liquid chromatography with a fluorescence detector. The excitation and emission are 346 and 420 nm, respectively. Mice: Test compounds are administered at a dose of 10 mg/kg as a cassette dosing to nonfasted mice (BALB/cAJcl; female). After oral administration, blood samples are collected. The blood samples are centrifuged to obtain the plasma fraction. The plasma samples are deproteinized with acetonitrile containing an internal standard. After centrifugation, the supernatant is diluted with a mixture of 0.01 M ammonium formate solution and acetonitrile (9:1, v/v) and centrifuged again. The compound concentrations in the supernatant are measured by LC/MS/MS[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.

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REFERENCES

[1]. Miyamoto N, et al. Discovery of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (TAK-593), a highly potent VEGFR2 kinase inhibitor. Bioorg Med Chem. 2013 Apr 15;21(8):2333-2345.

[2]. Awazu Y, et al. Anti-angiogenic and anti-tumor effects of TAK-593, a potent and selective inhibitor of vascular endothelial growth factor and platelet-derived growth factor receptor tyrosine kinase. Cancer Sci. 2013 Apr;104(4):486-94.

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