Axitinib

Cat. No.: HY-10065

CAS No.: 319460-85-0

Molecular Formula: $C_{22}H_{18}N_4OS$

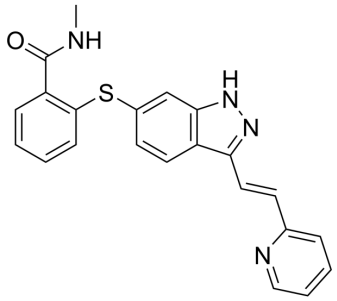
Molecular Weight: 386

Target: VEGFR; PDGFR

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 : 20.83 mg/mL (53.96 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5907 mL	12.9534 mL	25.9067 mL
	5 mM	0.5181 mL	2.5907 mL	5.1813 mL
	10 mM	0.2591 mL	1.2953 mL	2.5907 mL

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

In Vivo

1. Add each solvent one by one: 20% HP-β-CD/10 mM citrate pH 2.0
   Solubility: 8.33 mg/mL (21.58 mM); Clear solution; Need ultrasonic and adjust pH to 3 with H_2O
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (5.39 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.08 mg/mL (5.39 mM); Suspended solution; Need ultrasonic
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.39 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Axitinib is a multi-targeted tyrosine kinase inhibitor with IC_{50}s of 0.1, 0.2, 0.1-0.3, 1.6 nM for VEGFR1, VEGFR2, VEGFR3 and PDGFRβ, respectively.

IC_{50} & Target	VEGFR1	VEGFR2	VEGFR3	PDGFRβ
	0.1 nM (IC_{50})	0.2 nM (IC_{50})	0.1 nM (IC_{50})	1.6 nM (IC_{50})

In Vitro	Axitinib (AG-013736) is a potent and selective inhibitor of VEGFR 1 to 3. In transfected or endogenous RTK-expressing cells, Axitinib potently blocks growth factor-stimulated phosphorylation of VEGFR-2 and VEGFR-3 with average IC_{50} values of 0.2 and 0.1 to 0.3 nM, respectively. Cellular activity against VEGFR-1 is 1.2 nM (measured in the presence of 2.3% bovine serum albumin), equivalent to an absolute IC_{50} of ~0.1 nM, based on protein binding of Axitinib. The potency against murine VEGFR-2 (Flk-1) in Flk-1-transfected NIH-3T3 cells is 0.18 nM, similar to that of its human homologue. Axitinib shows ~8- to 25-fold higher IC_{50} against the closely related type III and V family RTKs, including PDGFR-β (1.6 nM), KIT (1.7 nM), and PDGFR-α (5 nM); nanomolar concentrations of Axitinib blocks PDGF BB-mediated human glioma U87MG cell (PDGFR-β-positive) migration but not proliferation[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	A single oral dose of Axitinib (100 mg/kg) markedly suppresses murine VEGFR-2 phosphorylation for up to 7 h compared with control tumors. Axitinib rapidly inhibits VEGF-induced vascular permeability in the skin of mice; the inhibition is dose-dependent and directly correlated with drug concentration in mice. Pharmacokinetic/pharmacodynamic analysis indicate an unbound EC_{50} of 0.46 nM. Similar inhibitory effects are also shown in the skin of MV522 tumor-bearing mice without exogenous VEGF-A stimulation. Axitinib inhibits the growth of human xenograft tumors in mice. Axitinib produces dose-dependent growth delay regardless of initial tumor size, model type, or implant site[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Endothelial or tumor cells are starved for 18 h in the presence of either 1% FBS (HUVEC) or 0.1% FBS (tumor cells). Axitinib is added and cells are incubated for 45 min at 37°C in the presence of 1 mM Na_3VO_4. The appropriate growth factor is added to the cells, and after 5 min, cells are rinsed with cold PBS and lysed in the lysis buffer and a protease inhibitor cocktail. The lysates are incubated with immunoprecipitation antibodies for the intended proteins overnight at 4°C. Antibody complexes are conjugated to protein A beads and supernatants are separated by SDS-PAGE[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice and Rats[2] Mice with M24met xenograft tumors (400-600 mm^3) are administered with a single dose of Axitinib or the control (0.5% carboxymethylcellulose/H_2O). Blood and tumor tissue samples are collected for pharmacokinetic and VEGFR-2 measurements. Total protein concentrations in tumor tissues are determined using the Bradford colorimetric assay. Six-day-old Sprague-Dawley rats are given two i.p. injections of Axitinib (30 mg/kg). Animals are sacrificed, retinas are collected and lysed, and immunoprecipitation/immunoblotting experiments are done. ECL-Plus is used for detection and densitometry analysis is done using the Alpha Imager 8800. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Metab. 2021 Sep 8;S1550-4131(21)00375-2.
- Cell Stem Cell. 2019 Sep 5;25(3):373-387.e9.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Adv Sci (Weinh). 2023 Apr 23;e2205915.
- Sci Total Environ. 2023 Aug 23;903:166505.

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REFERENCES

[1]. Fenton BM, et al. The addition of AG-013736 to rractionated radiation improves tumor response without functionally normalizing the tumor vasculature. Cancer Res. 2007 Oct 15;67(20):9921-8.

[2]. Hu-Lowe DD, et al. Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res. 2008 Nov 15;14(22):7272-83

[3]. Allen E, et al. Metabolic Symbiosis Enables Adaptive Resistance to Anti-angiogenic Therapy that Is Dependent on mTOR Signaling. Cell Rep. 2016 May 10;15(6):1144-60.

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