Tivozanib

Cat. No.: HY-10977

CAS No.: 475108-18-0

Molecular Formula: $C_{22}H_{19}ClN_4O_5$

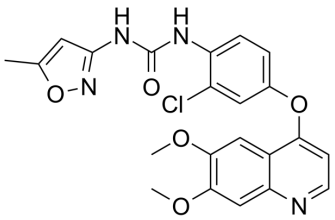
Molecular Weight: 454.86

Target: VEGFR

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 : 25 mg/mL (54.96 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1985 mL	10.9924 mL	21.9848 mL
	5 mM	0.4397 mL	2.1985 mL	4.3970 mL
	10 mM	0.2198 mL	1.0992 mL	2.1985 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: ≥ 2.5 mg/mL (5.50 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.50 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Tivozanib (AV-951; KRN951) is a potent and selective and orally active VEGFR tyrosine kinase inhibitor with IC_{50} of 0.21, 0.16, 0.24 nM for VEGFR-1, VEGFR-2, VEGFR-3, respectively. Tivozanib inhibits angiogenesis and vascular permeability in tumor tissues and shows antitumor activity. Tivozanib has the potential for the research of metastatic renal cell carcinoma (RCC) [1][2][3].

IC_{50} & Target

VEGFR1	VEGFR2	VEGFR3
0.21 nM (IC_{50})	0.16 nM (IC_{50})	0.24 nM (IC_{50})

In Vitro

Tivozanib inhibits the phosphorylation of VEGFR-1, VEGFR-2 and VEGFR-3[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	Tivozanib (1 mg/kg; p.o.; 14 days) suppresses the development of CNV lesions and leds to a significant regression of established CNV, reducing the affected areas by 67.7%[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay	Cell-free kinase assays are done in quadruplicate with 1 μM ATP to determine the IC_{50} values of KRN951 against a variety of recombinant receptor and nonreceptor tyrosine kinases[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cell-based assays are done to determine the ability of KRN951 to inhibit ligand-dependent phosphorylation of receptor tyrosine kinases. Briefly, the cells are starved overnight in appropriate basic medium containing 0.5% fetal bovine serum (FBS). Following the addition of KRN951 or 0.1% DMSO, the cells are incubated for 1 hour and then stimulated with the cognate ligand at 37°C. Receptor phosphorylation is induced for 5 minutes except for VEGFR3 (10 minutes), c-Met (10 minutes), and c-Kit (15 minutes). All the ligands used in the assays are human recombinant proteins, except for VEGF-C, a rat recombinant protein. Following cell lysis, receptors are immunoprecipitated with appropriate antibodies and subjected to immunoblotting with phosphotyrosine. Quantification of the blots and calculation of IC_{50} values are carried out[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: Cancer cells are s.c. inoculated into the right flank of the athymic rats. Once established, tumors of 1,500 mm^3 are surgically excised and smaller tumor fragments (20-30 mg) are s.c. implanted in the right flank of irradiated rats. Oral administration of KRN951 (0.2 or 1 mg/kg) or vehicle is initiated at the day of randomization (day 0). Tumor volume is measured twice weekly with Vernier calipers, and calculated[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Cancer Cell Int. 2021 Jun 5;21(1):291.
- Technical University of Munich. 24.01.2018.
- Patent. US20170349880A1.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Motzer RJ, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol. 2013 Oct 20;31(30):3791-9.

[2]. De Luca A, et al. Tivozanib, a pan-VEGFR tyrosine kinase inhibitor for the potential treatment of solid tumors. IDrugs. 2010 Sep;13(9):636-45.

[3]. Eskens FA, det al. Biologic and clinical activity of tivozanib (AV-951, KRN-951), a selective inhibitor of VEGF receptor-1, -2, and -3 tyrosine kinases, in a 4-week-on, 2-week-off schedule in patients with advanced solid tumors. Clin Cancer Res. 2011 Nov 15;17(22):7156-63.

[4]. Kang S, et al. Antiangiogenic effects of tivozanib, an oral VEGF receptor tyrosine kinase inhibitor, on experimental choroidal neovascularization in mice. Exp Eye Res. 2013 Jul;112:125-33.

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

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