Altiratinib

Cat. No.: HY-B0791

CAS No.: 1345847-93-9

Molecular Formula: $C_{26}H_{21}F_3N_4O_4$

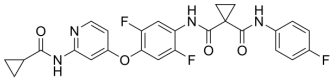
Molecular Weight: 510.46

Target: VEGFR; c-Met/HGFR; FLT3; Trk Receptor

Pathway: Protein Tyrosine Kinase/RTK; Neuronal Signaling

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 : 25 mg/mL (48.98 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9590 mL	9.7951 mL	19.5902 mL
	5 mM	0.3918 mL	1.9590 mL	3.9180 mL
	10 mM	0.1959 mL	0.9795 mL	1.9590 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 (4.90 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Altiratinib (DCC-2701) is a multi-targeted kinase inhibitor with IC_{50}s of 2.7, 8, 9.2, 9.3, 0.85, 4.6, 0.83 nM for MET, TIE2, VEGFR2 , FLT3, Trk1, Trk2, and Trk3 respectively.

IC_{50} & Target

VEGFR2 9.2 nM (IC_{50})	Trk1 0.85 nM (IC_{50})	Trk2 4.6 nM (IC_{50})	Trk3 0.93 nM (IC_{50})
MET 2.7 nM (IC_{50})	TIE2 8 nM (IC_{50})	FLT3 9.3 nM (IC_{50})	

In Vitro

Altiratinib also inhibits MET isoforms MET^{D1228H}, MET^{D1228N}, MET^{Y1230C}, MET^{Y1230D}, MET^{Y1230H}, MET^{M1250T} with IC_{50}s of 3.6, 1.3, 1.2, 0.37, 1.5 and 6 nM, respectively. Altiratinib inhibits MET phosphorylation with IC_{50} values of 0.85 and 2.2 nM, respectively. In the U-87 glioblastoma cell line, MET and HGF are both expressed. Altiratinib blocks autocrine activation of

	MET phosphorylation in these cells (IC_{50}=6.2 nM). Altiratinib potently inhibits cellular proliferation in MET-amplified EBC-1 and MKN-45 cells, as well as TPM3-TRKA fusion KM-12 cells. Activation of MET is known to increase the motility and invasiveness of cancer cells: Altiratinib inhibits HGF-induced A549 cell migration, with an IC_{50} of 13 nM. Altiratinib also inhibits FLT3-ITD mutant MV-4-11 cell proliferation with an IC_{50} of 12 nM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	A single oral dose of 30 mg/kg Altiratinib leads to >95% inhibition of MET phosphorylation for the entire 24-hour period. A single 10 mg/kg oral dose of Altiratinib exhibits complete inhibition of MET phosphorylation through 12 hours and 73% inhibition at 24 hours postdose. Altiratinib dosed at 10 mg/kg twice a day leads to a significant 90% decrease in BLI signal. Altiratinib exhibits properties amenable to oral administration and exhibits substantial blood–brain barrier penetration, an attribute of significance for eventual treatment of brain cancers and brain metastases[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Altiratinib is dispensed into assay plates. Cells are added to 96-well (EBC-1, M-NFS-60, and SK-MEL-28: 2,500 cells/well; MKN-45: 5,000 cells/well; MV-4-11: 10,000 cells/well) or 384-well plates (A375 and HCT-116: 625 cells/well; BT-474, KM-12, PC-3, and U-87-MG: 1,250 cells/well). Plates are incubated for 72 hours. Viable cells are quantified using resazurin using a plate reader with excitation at 540 nm and emission at 600 nm[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: Female nude mice are inoculated subcutaneously. On days 9 to 10, when tumor volumes reached 326 mg on average, mice are randomly assigned to groups and dosed once orally with 0.4% HMPC, (n=3); Altiratinib at 30 mg/kg (n=21); or Altiratinib at 10 mg/kg (n=21). At specified time points, whole blood and tumors are collected. Pharmacokinetic analysis is performed. Tumor samples are processed in the Western blot assay methods[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Patent. US20170349880A1.

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REFERENCES

[1]. Smith BD, et al. Altiratinib Inhibits Tumor Growth, Invasion, Angiogenesis, and Microenvironment-Mediated DrugResistance via Balanced Inhibition of MET, TIE2, and VEGFR2. Mol Cancer Ther. 2015 Sep;14(9):2023-34.

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