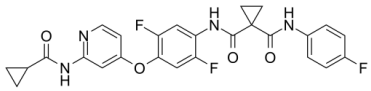
Data Sheet

Product Name:	Altiratinib
Cat. No.:	CS-3944
CAS No.:	1345847-93-9
Molecular Formula:	C26H21F3N4O4
Molecular Weight:	510.46
Target:	c-Met/HGFR; FLT3; Trk Receptor; VEGFR
Pathway:	Neuronal Signaling; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 33 mg/mL (64.65 mM)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 2.7 nM (MET), 8 nM (TIE2), 9.2 nM (VEGFR2), 9.3 nM (FLT3), 0.85 nM (Trk1), 4.6 nM (Trk2), 0.93 nM (Trk3)[1] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: Altiratinib is prepared in DMSO[1].[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]. **Animal Administration:** Altiratinib is prepared in 0.4% HMPC[1].[1]Mouse: 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].

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.

CAIndexNames:

1,1-Cyclopropanedicarboxamide, N-[4-[[2-[(cyclopropylcarbonyl)amino]-4-pyridinyl]oxy]-2,5-difluorophenyl]-N'-(4-fluorophenyl)-

SMILES:

O=C(C1(C(NC2=CC=C(F)C=C2)=O)CC1)NC3=CC(F)=C(OC4=CC(NC(C5CC5)=O)=NC=C4)C=C3F

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