Motesanib

Cat. No.: HY-10228

CAS No.: 453562-69-1

Molecular Formula: $C_{22}H_{23}N_5O$

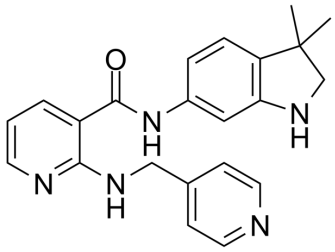
Molecular Weight: 373.45

Target: c-Kit; 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 : ≥ 100 mg/mL (267.77 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6777 mL	13.3887 mL	26.7773 mL
	5 mM	0.5355 mL	2.6777 mL	5.3555 mL
	10 mM	0.2678 mL	1.3389 mL	2.6777 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 (6.69 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.69 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Motesanib (AMG 706) is a potent ATP-competitive inhibitor of VEGFR1/2/3 with IC_{50}s of 2 nM/3 nM/6 nM, respectively, and has similar activity against Kit, and is appr 10-fold more selective for VEGFR than PDGFR and Ret.

IC_{50} & Target

VEGFR1	VEGFR2	VEGFR3
2 nM (IC_{50})	3 nM (IC_{50})	6 nM (IC_{50})

In Vitro

Motesanib has broad activity against the human VEGFR family, and displays > 1000 selectivity against EGFR, Src, and p38 kinase. Motesanib significantly inhibits VEGF-induced cellular proliferation of HUVECs with an IC_{50} of 10 nM, while displaying little effect at bFGF-induced proliferation with an IC_{50} of >3,000 nM. Motesanib also potently inhibits PDGF-induced

	proliferation and SCF-induced c-kit phosphorylation with IC_{50} of 207 nM and 37 nM, respectively, but not effective against the EGF-induced EGFR phosphorylation and cell viability of A431 cells[1]. Althouth displaying little antiproliferative activity on cell growth of HUVECs alone, Motesanib treatment significantly sensitizes the cells to fractionated radiation[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Motesanib (100 mg/kg) significantly inhibits VEGF-induced vascular permeability in a time-dependent manner. Oral administration of Motesanib twice daily or once daily potently inhibits, in a dose-dependent manner, VEGF-induced angiogenesis using the rat corneal model with ED_{50} of 2.1 mg/kg and 4.9 mg/kg, respectively. Motesanib induces a dose-dependent tumor regression of established A431 xenografts by selectively targeting neovascularization in tumor cells[1]. Motesanib in combination with radiation displays significant anti-tumor activity in head and neck squamous cell carcinoma (HNSCC) xenograft models[2]. Motesanib treatment also induces significant dose-dependent reductions in tumor growth and blood vessel density of MCF-7, MDA-MB-231, or Cal-51 xenografts, which can be markedly enhanced when combined with docetaxel or tamoxifen[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Optimal enzyme, ATP, and substrate (gastrin peptide) concentrations are established for each enzyme using homogeneous time-resolved fluorescence (HTRF) assays. Motesanib is tested in a 10-point dose-response curve for each enzyme using an ATP concentration of two-thirds K_m for each. Most assays consist of enzyme mixed with kinase reaction buffer [20 mM Tris-HCl (pH 7.5), 10 mM $MgCl_2$, 5 mM $MnCl_2$, 100 mM NaCl, 1.5 mM EGTA]. A final concentration of 1 mM DTT, 0.2 mM $NaVO_4$, and 20 μg/mL BSA is added before each assay. For all assays, 5.75 mg/mL streptavidin-allophycocyanin and 0.1125 nM Eu-PT66 are added immediately before the HTRF reaction. Plates are incubated for 30 minutes at room temperature and read on a Discovery instrument. IC_{50} values are calculated using the Levenberg-Marquardt algorithm into a four-parameter logistic equation. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cells are preincubated for 2 hours with different concentrations of Motesanib, and exposed with 50 ng/mL VEGF or 20 ng/mL bFGF for an additional 72 hours. Cells are washed twice with DPBS, and plates are frozen at -70°C for 24 hours. Proliferation is assessed by the addition of CyQuant dye, and plates are read on a Victor 1420 workstation. IC_{50} data are calculated using the Levenberg-Marquardt algorithm into a four-parameter logistic equatio. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	A431 cells are cultured in DMEM (low glucose) with 10% FBS and penicillin/streptomycin/glutamine. Cells are harvested by trypsinization, washed, and adjusted to a concentration of 5×10^7/mL in serum-free medium. Animals are challenged s.c. with 1×10^7 cells in 0.2 mL over the left flank. Approximately 10 days thereafter, mice are randomized based on initial tumor volume measurements and treated with either vehicle (Ora-Plus) or Motesanib. Tumor volumes and body weights are recorded twice weekly and/or on the day of sacrifice. Tumor volume is measured with a Pro-Max electronic digital caliper and calculated using the formula length (mm)×width (mm)×height (mm) and expressed in mm^3. Data are expressed as mean±SE. Repeated measures ANOVA followed by Scheffe post hoc testing for multiple comparisons is used to evaluate the statistical significance of observed differences. 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.
- J Cell Biochem. 2020 Mar;121(3):2343-2353.
- Cell Physiol Biochem. 2018;48(1):227-236.

- Oncotarget. 2016 Sep 27;7(39):63839-63855.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Polverino A, et al. AMG 706, an oral, multikinase inhibitor that selectively targets vascular endothelial growth factor, platelet-derived growth factor, and kit receptors, potently inhibits angiogenesis and induces regression in tumor xenografts. Cancer R

[2]. Kruser TJ, et al. Augmentation of radiation response by motesanib, a multikinase inhibitor that targets vascular endothelial growth factor receptors. Clin Cancer Res, 2010, 16(14), 3639-3647.

[3]. Coxon A, et al. Broad antitumor activity in breast cancer xenografts by motesanib, a highly selective, oral inhibitor of vascular endothelial growth factor, platelet-derived growth factor, and Kit receptors. Clin Cancer Res, 2009, 15(1), 110-118.

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

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA