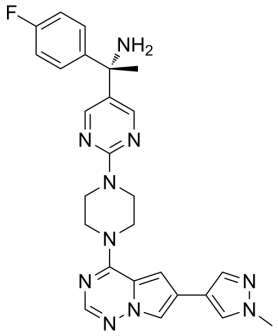
Avapritinib



Cat. No.:	HY-101561
CAS No.:	1703793-34-3
Molecular Formula:	$C_{26}H_{27}FN_{10}$
Molecular Weight:	498.56
Target:	c-Kit; PDGFR
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 1 year -20°C 6 months

SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 83.33 mg/mL (167.14 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0058 mL	10.0289 mL	20.0578 mL
5 mM	0.4012 mL	2.0058 mL	4.0116 mL
10 mM	0.2006 mL	1.0029 mL	2.0058 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 (5.01 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.01 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.01 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Avapritinib (BLU-285) is a highly potent, selective, and orally active KIT and PDGFRA activation loop mutant kinases inhibitor with IC_{50}s of 0.27 and 0.24 nM for KIT D816V and PDGFRA D842V, respectively. Avapritinib (BLU-285) binds the active conformation of the kinase and shows antitumor activity. Avapritinib (BLU-285) attenuates the transport function of both ABCB1 and ABCG2[1][2].

IC_{50} & Target

IC50: 0.27 nM (KIT D816V), 0.24 nM (PDGFRA D842V)[1]

In Vitro	Avapritinib (BLU-285) has demonstrated biochemical in vitro activity on the KIT exon 17 mutant enzyme, KIT D816V (IC_{50} =0.27 nM). Cellular activity of Avapritinib on KIT D816 mutants is measured by autophosphorylation in the human mast cell leukemia cell line HMC1.2, and the P815 mouse mastocytoma cell line with IC_{50}=4 and 22 nM, respectively. In Kasumi-1 cells, a t(8;21)-positive AML cell line with a KIT exon 17 N822K mutation, Avapritinib potently inhibits KIT N822K mutant autophosphorylation (IC_{50}=40 nM), downstream signaling, as well as cellular proliferation (IC_{50}=75 nM)[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In vivo Avapritinib (BLU-285) is well tolerated and has demonstrated dose dependent antitumor efficacy. Complete tumor growth inhibition and ≥75% KIT kinase inhibition is observed with 10 mg/kg once daily, oral dosing of Avapritinib in the aggressive KIT exon 17 mutant driven P815 mastocytoma model grown as a solid tumor allograft as well as in a disseminated model of disease. Disease burden, measured by whole body luciferase imaging (photons/second/mm^2), increases 86-fold in the vehicle control animals over the 24 day dosing period with widespread disease detectable in both femurs, the pelvis and circulating in peripheral blood. Avapritinib at both doses (10 or 30 mg/kg orally, once daily) results in a marked reduction of disease burden throughout the study. Avapritinib at either 10 or 30 mg/kg results in tumor regression in all animals with disease abrogation indistinguishable from background signal measurements in several animals by the end of study. Avapritinib is also well tolerated in this in vivo model and has no adverse effects on body weight at either dose [3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice[1] A Kasumi-1 luc^+ AML NOG SCID mouse femoral injection model is used to assess the efficacy of Avapritinib (BLU-285) in KIT exon 17-mutated CBF-AML. Following a 21 day post injection latency period, mice are dosed with Avapritinib orally, once daily at 10 mg/kg or 30 mg/kg through day 45. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Biomaterials. 16 September 2022.
- Mol Pharmacol. April 5, 2022.
- SSRN. 2023 Aug 14.
- Major in Cancer Biology. 2019 Aug.

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REFERENCES

[1]. Wu CP, et al. Avapritinib: A Selective Inhibitor of KIT and PDGFRα that Reverses ABCB1 and ABCG2-MediatedMultidrug Resistance in Cancer Cell Lines. Mol Pharm. 2019 Jul 1;16(7):3040-3052.

[2]. Evans EK, et al. A precision therapy against cancers driven by KIT/PDGFRA mutations. Sci Transl Med. 2017 Nov 1;9(414). pii: eaao1690.

[3]. Erica Evans, et al. Blu-285, a Potent and Selective Inhibitor for Hematologic Malignancies with KIT Exon 17 Mutations.Blood 2015 126:568.

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