Brigatinib

Cat. No.: HY-12857

CAS No.: 1197953-54-0

Molecular Formula: $C_{29}H_{39}ClN_7O_2P$

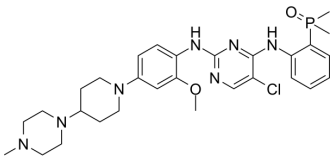
Molecular Weight: 584.09

Target: Anaplastic lymphoma kinase (ALK)

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

Ethanol : 10 mg/mL (17.12 mM; Need ultrasonic and warming)
DMSO : 2 mg/mL (3.42 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7121 mL	8.5603 mL	17.1206 mL
5 mM	0.3424 mL	1.7121 mL	3.4241 mL
10 mM	0.1712 mL	0.8560 mL	1.7121 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% EtOH >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1 mg/mL (1.71 mM); Clear solution
2. Add each solvent one by one: 10% EtOH >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1 mg/mL (1.71 mM); Clear solution
3. Add each solvent one by one: 10% EtOH >> 90% corn oil
   Solubility: ≥ 1 mg/mL (1.71 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 0.5 mg/mL (0.86 mM); Clear solution
5. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.5 mg/mL (0.86 mM); Clear solution
6. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.5 mg/mL (0.86 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	Brigatinib (AP-26113) is a highly potent, selective and orally active ALK inhibitor, with an IC_{50} of 0.6 nM. Brigatinib can be used for research of NSCLC[1].
IC_{50} & Target	IC50: 0.6 nM (ALK)[1]
In Vitro	Brigatinib potently inhibits the in vitro kinase activity of ALK (IC_{50}, 0.6 nM) and all five mutant variants tested, including G1202R (IC_{50}, 0.6-6.6 nM). Brigatinib demonstrates a high degree of selectivity, only inhibiting 11 additional native or mutant kinases with IC_{50} <10 nM. These include ROS1, FLT3, and mutant variants of FLT3 (D835Y) and EGFR (L858R; IC_{50}, 1.5-2.1 nM). Brigatinib exhibits more modest activity against EGFR with a T790M resistance mutation (L858R/T790M), native EGFR, IGF1R, and INSR (IC_{50}, 29-160 nM) and does not inhibit MET (IC_{50} >1000 nM). In cellular assays, brigatinib inhibits ALK and ROS1 with IC_{50}s of 14 and 18 nM, respectively. Brigatinib inhibits FLT3 and IGF-1R with about 11-fold lower potency (IC_{50}, 148-158 nM) and inhibits mutant variants of FLT3 and EGFR with 15- to 35-fold lower potency (IC_{50}, 211-489 nM). Brigatinib inhibits cell growth with GI_{50} values ranging from 503 to 2,387 nM in three ALK-negative ALCL and NSCLC cell lines[1]. Brigatinib inhibits ALK activity and abrogates proliferation of ALK addicted neuroblastoma cell lines, with IC_{50} of 75.27 ± 8.89 nM. Brigatinib inhibits both the ALK-I1171N and the ALK-G1269A mutant receptors at 10 and 4 nM levels, respectively[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Brigatinib (10, 25, or 50 mg/kg once daily, p.o.) leads to a dose-dependent inhibition of tumor growth in ALK^+ Karpas-299 (ALCL) and H2228 (NSCLC) xenograft mouse models. Brigatinib markedly enhances survival of mice bearing ALK^+ brain tumors compared with PF-02341066[1]. Brigatinib (10, 25, 50 mg/kg, p.o.) results in dose-dependent antitumor activity, with tumor regressions in a mouse model of NSCLC[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	In vitro HotSpot^{SM} kinase profiling of 289 kinases is performed. The assay is conducted in the presence of 10 μM [^{33}P]-ATP, using brigatinib concentrations ranging from 0.05 nM to 1 μM. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [3]	Cells are seeded at 15,000 per well with serial dilutions of the indicated inhibitors. After 72 hours cell viability is assessed by resazurin. IC_{50} values are calculated with GraphPad Prism 6.0 by fitting data to a log (inhibitor concentration) vs. normalized response (variable slope) equation. Each experiment is performed in duplicate and repeated at least three times. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice: (1) Eight- to 10-week-old female SCID/beige mice are injected intravenously with 5×10^6 H3122 cells per mouse and are randomly selected into treatment groups (n=10) when the average tumor size reaches appr 300 mm^3 (day zero). Treatments are administered orally for up to 21 consecutive days at a 10 mL/kg dose volume. Subcutaneous tumors are measured two or three times weekly. Tumor volume (in mm^3) is calculated using the formula $(L\times W^2)/2$. When a tumor reaches 10% of the body weight of the host, the animal is euthanized via CO_2 asphyxiation. (2) Eight- to 10-week old female SCID/beige mice are injected subcutaneously with 2.5×10^6 Karpas-299 cells per mouse and are randomly selected into treatment groups (n=10) when the average tumor size reached appr 180 mm^3 (day zero). Treatments are administered orally for 14 consecutive days at a 10 mL/kg dose volume. Tumor volume is measured and calculated as described for the H3122 model. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Discov. 2018 Jun;8(6):714-729.
- Nat Cancer. 2022 Jun 20.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Cell Rep Med. 2023 Jan 10;100911.
- Theranostics. 2019 Jul 9;9(17):4878-4892.

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REFERENCES

[1]. Zhang S, et al. The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models. Clin Cancer Res. 2016 Nov 15;22(22):5527-5538

[2]. Huang WS, et al. Discovery of Brigatinib (AP26113), a Phosphine Oxide-Containing, Potent, Orally Active Inhibitor of Anaplastic Lymphoma Kinase. J Med Chem. 2016 May 26;59(10):4948-64.

[3]. Siaw JT, et al. Brigatinib, an anaplastic lymphoma kinase inhibitor, abrogates activity and growth in ALK-positive neuroblastoma cells, Drosophila and mice. Oncotarget. 2016 May 17;7(20):29011-22

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