Gilteritinib hemifumarate

Cat. No.: HY-12432A

CAS No.: 1254053-84-3

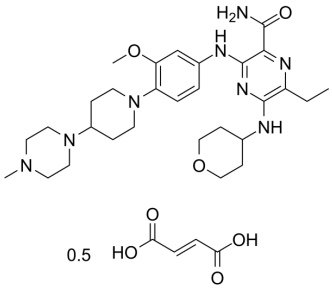
Molecular Formula: $C_{29}H_{44}N_8O_{3\ 0.5}C_4H_4O_4$

Molecular Weight: 610.75

Target: FLT3; TAM Receptor

Pathway: Protein Tyrosine Kinase/RTK

Storage: 4°C, stored under nitrogen
* In solvent : -80°C, 6 months; -20°C, 1 month (stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 6.67 mg/mL (10.92 mM; ultrasonic and warming and heat to 70°C)
H_2O : 2 mg/mL (3.27 mM; Need ultrasonic)

Preparing Stock Solutions

Mass / Solvent / Concentration	1 mg	5 mg	10 mg
1 mM	1.6373 mL	8.1867 mL	16.3733 mL
5 mM	0.3275 mL	1.6373 mL	3.2747 mL
10 mM	0.1637 mL	0.8187 mL	1.6373 mL

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 10 mg/mL (16.37 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: Saline
   Solubility: 0.5 mg/mL (0.82 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Gilteritinib (ASP2215) hemifumarate is a potent and ATP-competitive FLT3/AXL inhibitor with IC_{50} of 0.29 nM/0.73 nM, respectively.

IC_{50} & Target

IC50: 0.29 nM (FLT3)[1]
IC50: 0.35 nM (LTK), 0.73 nM (AXL), 1.2 nM (EML4-ALK), 230 nM (c-KIT)[2]

In Vitro

Of the 78 tyrosine kinases tested, Gilteritinib (ASP2215) inhibits FLT3, leukocyte tyrosine kinase (LTK), anaplastic lymphoma kinase (ALK), and AXL kinases by over 50% at 1 nM with an IC_{50} value of 0.29 nM for FLT3, approximately 800-fold more potent than for c-KIT[1]. Gilteritinib inhibits the activity of eight of the 78 tested kinases by over 50% at concentrations of either 1 nM (FLT3, LTK, ALK, and AXL) or 5 nM (TRKA, ROS, RET, and MER). The IC_{50}s are 0.29 nM for FLT3 and 0.73 nM for AXL.

	Gilteritinib inhibits FLT3 at an IC_{50} that is approximately 800-fold more potent than the concentration required to inhibit c-KIT (230 nM). The antiproliferative activity of Gilteritinib is evaluated against MV4-11 and MOLM-13 cells, which endogenously express FLT3-ITD. After 5 days of treatment, Gilteritinib inhibits the growth of MV4-11 and MOLM-13 cells with mean IC_{50}s of 0.92 nM (95% CI: 0.23-3.6 nM) and 2.9 nM (95% CI: 1.4-5.8 nM), respectively. Growth suppression of MV4-11 cells is accompanied by inhibition of FLT3 phosphorylation. Relative to vehicle control cells, phosphorylated FLT3 levels are 57%, 8%, and 1% after 2 h of treatment with 0.1 nM, 1 nM, and 10 nM Gilteritinib, respectively. In addition, doses as low as 0.1 nM or 1 nM result in the suppression of phosphorylated ERK, STAT5, and AKT, all of which are downstream targets of FLT3 activation. To investigate the effects of Gilteritinib on AXL inhibition, MV4-11 cells that expressed exogenous AXL are treated with Gilteritinib. At concentrations of 1 nM, 10 nM, and 100 nM for 4 h, Gilteritinib treatment decreases phosphorylated AXL levels by 38%, 29%, and 22%, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In MV4-11 xenografted-mice, the concentration of Gilteritinib (ASP2215) in tumors is more than 20-fold higher than that in plasma with oral administration of Gilteritinib at 10 mg/kg for 4 days. Treatment of Gilteritinib for 28 days results in dose-dependent inhibition of MV4-11 tumor growth and induces complete tumor regression at more than 6 mg/kg. Further, Gilteritinib decreases tumor burden in bone marrow and prolonged the survival of mice intravenously transplanted with MV4-11 cells[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	The kinase inhibitory activity of Gilteritinib is tested against a panel of 78 tested kinases using ATP concentrations that are approximately equal to the K_m value for each kinase in a TK-ELISA or off-chip mobility shift assay. Initially, two concentrations of Gilteritinib (1 nM and 5 nM) are tested to assess each compound's inhibitory effect on TK activity. Further studies are then conducted using a dose range of Gilteritinib to determine IC_{50} values for kinases in which activity is inhibited by >50% with 1 nM Gilteritinib as well as for c-KIT. TK-ELISA and MSA assays are used to conduct IC_{50} studies for FLT3, LTK, AXL, and c-KIT; the HTRF KinEASE-TK assay is performed to assess the IC_{50} value of echinoderm microtubule-associated protein-like 4-ALK (EML4-ALK)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	The effect of Gilteritinib on MV4-11 and MOLM-13 cells is assessed using the CellTiter-Glo Luminescent Cell Viability Assay. Subsequent studies are conducted to examine the effect of Gilteritinib and Quizartinib on Ba/F3 cells expressing either FLT3-ITD, FLT3-D835Y, FLT3-ITD-D835Y, FLT3-ITD-F691 L, or FLT3-ITD-F691I. MV4-11 and MOLM-13 cells are treated with DMSO or increasing concentrations of Gilteritinib (0.01, 0.1, 1, 10, and 100 nM) for 5 days, and cell viability is measured using CellTiter-Glo[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Antitumor activity is evaluated in nude mice transplanted with MV4-11 AML cells. The pharmacokinetics in xenografted mice is also investigated. MV4-11 xenografted-mice are treated with oral administration of Gilteritinib at 10 mg/kg for 4 days. Treatment of Gilteritinib for 28 days results in dose-dependent inhibition of MV4-11 tumor growth and induces complete tumor regression at more than 6 mg/kg[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Cancer Discov. 2023 Apr 3;CD-22-0411.
- Sci Adv. 2022 Sep 16;8(37):eabp9005.

- Blood Cancer J. 2022 Jan 11;12(1):5.
- Haematologica. 2018 Nov;103(11):1862-1872.

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REFERENCES

[1]. ASP2215, a novel FLT3/AXL inhibitor: Preclinical evaluation in acute myeloid leukemia (AML). 2014 ASCO Annual Meeting.

[2]. Mori M, et al. Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. Invest New Drugs. 2017 Oct;35(5):556-565.

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