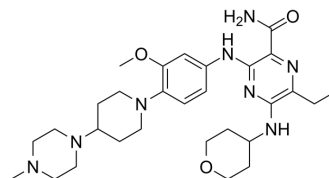


Gilteritinib

Cat. No.:	HY-12432
CAS No.:	1254053-43-4
Molecular Formula:	C ₂₉ H ₄₄ N ₈ O ₃
Molecular Weight:	552.71
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	Ethanol : 100 mg/mL (180.93 mM; ultrasonic and adjust pH to 2 with HCl)																									
	DMSO : 2 mg/mL (3.62 mM; Need ultrasonic)																									
	<table border="1"> <thead> <tr> <th rowspan="2">Solvent</th> <th rowspan="2">Mass</th> <th colspan="3">Concentration</th> </tr> <tr> <th>1 mg</th> <th>5 mg</th> <th>10 mg</th> </tr> </thead> <tbody> <tr> <td rowspan="4">Preparing Stock Solutions</td> <td>1 mM</td> <td>1.8093 mL</td> <td>9.0463 mL</td> <td>18.0927 mL</td> </tr> <tr> <td>5 mM</td> <td>0.3619 mL</td> <td>1.8093 mL</td> <td>3.6185 mL</td> </tr> <tr> <td>10 mM</td> <td>0.1809 mL</td> <td>0.9046 mL</td> <td>1.8093 mL</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Solvent	Mass	Concentration			1 mg	5 mg	10 mg	Preparing Stock Solutions	1 mM	1.8093 mL	9.0463 mL	18.0927 mL	5 mM	0.3619 mL	1.8093 mL	3.6185 mL	10 mM	0.1809 mL	0.9046 mL	1.8093 mL				
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	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 (18.09 mM); Suspended solution; Need ultrasonic																									

BIOLOGICAL ACTIVITY

Description	Gilteritinib (ASP2215) is a potent and ATP-competitive FLT3/AXL inhibitor with IC ₅₀ s of 0.29 nM/0.73 nM, respectively.
IC ₅₀ & Target	IC ₅₀ : 0.29 nM (FLT3) ^[1] IC ₅₀ : 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].

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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].

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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.

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

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