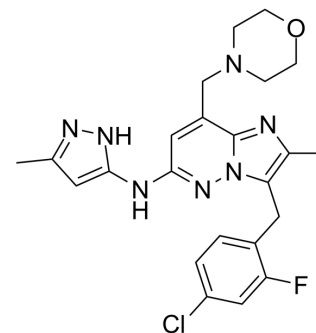


Gandotinib

Cat. No.:	HY-13034												
CAS No.:	1229236-86-5												
Molecular Formula:	C ₂₃ H ₂₅ ClFN ₇ O												
Molecular Weight:	469.94												
Target:	JAK; FLT3; FGFR; VEGFR												
Pathway:	Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt												
Storage:	<table border="0"> <tr> <td>Powder</td> <td>-20°C</td> <td>3 years</td> </tr> <tr> <td></td> <td>4°C</td> <td>2 years</td> </tr> <tr> <td>In solvent</td> <td>-80°C</td> <td>2 years</td> </tr> <tr> <td></td> <td>-20°C</td> <td>1 year</td> </tr> </table>	Powder	-20°C	3 years		4°C	2 years	In solvent	-80°C	2 years		-20°C	1 year
Powder	-20°C	3 years											
	4°C	2 years											
In solvent	-80°C	2 years											
	-20°C	1 year											



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 50 mg/mL (106.40 mM)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent		Mass		
	Concentration		1 mg	5 mg	10 mg
	1 mM		2.1279 mL	10.6397 mL	21.2793 mL
	5 mM		0.4256 mL	2.1279 mL	4.2559 mL
	10 mM		0.2128 mL	1.0640 mL	2.1279 mL

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

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
 Solubility: ≥ 2.5 mg/mL (5.32 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
 Solubility: ≥ 2.5 mg/mL (5.32 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Gandotinib (LY2784544) is a potent JAK2 inhibitor with IC₅₀ of 3 nM. Gandotinib (LY2784544) also inhibits FLT3, FLT4, FGFR2, TYK2, and TRKB with IC₅₀ of 4, 25, 32, 44, and 95 nM.

IC₅₀ & Target

JAK2 3 nM (IC ₅₀)	Tyk2 44 nM (IC ₅₀)	JAK3 48 nM (IC ₅₀)	FGFR2 32 nM (IC ₅₀)
FGFR3 106 nM (IC ₅₀)	Flt-4 25 nM (IC ₅₀)	KDR 109 nM (IC ₅₀)	FLT3 4 nM (IC ₅₀)

	TRKB 95 nM (IC ₅₀)	ALK 138 nM (IC ₅₀)	MUSK 147 nM (IC ₅₀)	AURKA 168 nM (IC ₅₀)
	MAP3K9 299 nM (IC ₅₀)			
In Vitro	<p>Gandotinib (LY2784544), a potent, selective and ATP-competitive inhibitor of janus kinase 2 (JAK2) tyrosine kinase. LY2784544 effectively inhibits JAK2V617F-driven signaling and cell proliferation in Ba/F3 cells (IC₅₀=20 and 55 nM, respectively). In comparison, Gandotinib (LY2784544) is much less potent at inhibiting interleukin-3-stimulated wild-type JAK2-mediated signaling and cell proliferation (IC₅₀=1183 and 1309 nM, respectively). Gandotinib (LY2784544) potently inhibits the JAK2V617F signaling (IC₅₀=20 nM) but, remarkably, shows very minimal activity against the IL-3-activated wild-type JAK2 signaling with an IC₅₀ of 1183 nM. LY2784544 inhibits the proliferation of JAK2V617F-expressing cells (IC₅₀=55 nM) and is markedly less potent as an inhibitor of the proliferation of IL-3-stimulated wild-type JAK2 expressing Ba/F3 cells (IC₅₀=1309 nM). Gandotinib (LY2784544) is potent in the cell-based TF-1 JAK2 assay (IC₅₀=45 nM) and had the desired threshold selectivity in the NK-92 JAK3/JAK1 heterodimer assay (942 nM)^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>			
In Vivo	<p>Gandotinib (LY2784544) effectively inhibits STAT5 phosphorylation in Ba/F3-JAK2V617F-GFP (green fluorescent protein) ascitic tumor cells (TED₅₀=12.7 mg/kg) and significantly reduces (P<0.05) Ba/F3-JAK2V617F-GFP tumor burden in the JAK2V617F-induced MPN model (TED₅₀=13.7 mg/kg, twice daily)^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>			

PROTOCOL

Cell Assay ^[1]

Ba/F3 cells expressing JAK2V617F are placed in RPMI-1640-containing vehicle (DMSO) or Gandotinib (LY2784544) (concentration range, 0.001-20 μM) (1×10⁴ cells/96-well). Ba/F3 cells expressing wild-type JAK2 are treated similarly except IL-3 (2 ng/mL) is added. After a 72-hour incubation, cell proliferation is assessed by adding Cell Titer 96 Aqueous One Solution Reagent (20 μL/well). The IC₅₀ for inhibition of cell proliferation is calculated using the GraphPad Prism 4 software ^[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Administration ^[1]

Mice^[1]

Dose- and time-dependent in vivo inhibition of JAK2V617F signaling is assessed by measuring inhibition of STAT5 phosphorylation in a mouse ascitic tumor model. Ba/F3-JAK2V617F-GFP cells (1×10⁷) are implanted in the intraperitoneal cavity of severe combined immunodeficiency mice (SCID mice) and allowed to develop into ascitic tumors for 7 days. For dose-response studies (six animals/group), Gandotinib (LY2784544) is administered once by oral gavage (2.5, 5, 10, 20, 40, or 80 mg/kg), then 30 min later, ascitic tumor cells are collected, fixed, incubated for 2 h with Mouse-anti-pSTAT5 (pY694) Alexa Fluor 647 (1:10 dilution), and analyzed by flow cytometry. Time course studies are performed similarly, except the animals are treated with Gandotinib (LY2784544) at 20, 40 or 80 mg/kg and ascitic tumor cells collected at prespecified intervals of 0.25-6 h after dosing. Data are analyzed by the one-way analysis of variance, and Dunnett's test (α=0.05). Dose response data are analyzed with a four-parameter logistic curve-fitting program.

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.
- Biol Pharm Bull. 2019 Aug 1;42(8):1415-1418.
- Patent. US20180263995A1.

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REFERENCES

[1]. Ma L, et al. Discovery and characterization of LY2784544, a small-molecule tyrosine kinase inhibitor of JAK2V617F. Blood Cancer J. 2013, 3, e109.

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

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