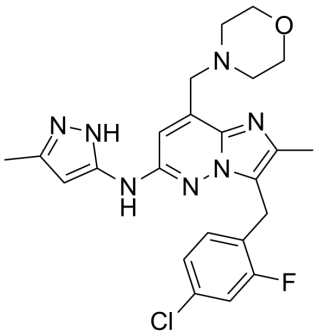
Gandotinib



Cat. No.:	HY-13034
CAS No.:	1229236-86-5
Molecular Formula:	$C_{23}H_{25}ClFN_7O$
Molecular Weight:	469.94
Target:	JAK; FLT3; FGFR; VEGFR
Pathway:	Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt
Storage:	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

1. 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
2. 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 IC_{50} of 3 nM. Gandotinib (LY2784544) also inhibits FLT3, FLT4, FGFR2, TYK2, and TRKB with IC_{50} of 4, 25, 32, 44, and 95 nM.

IC_{50} & 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

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 (IC_{50}=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 (IC_{50}=1183 and 1309 nM, respectively). Gandotinib (LY2784544) potently inhibits the JAK2V617F signaling (IC_{50}=20 nM) but, remarkably, shows very minimal activity against the IL-3-activated wild-type JAK2 signaling with an IC_{50} of 1183 nM. LY2784544 inhibits the proliferation of JAK2V617F-expressing cells (IC_{50}=55 nM) and is markedly less potent as an inhibitor of the proliferation of IL-3-stimulated wild-type JAK2 expressing Ba/F3 cells (IC_{50} =1309 nM). Gandotinib (LY2784544) is potent in the cell-based TF-1 JAK2 assay (IC_{50}=45 nM) and had the desired threshold selectivity in the NK-92 JAK3/JAK1 heterodimer assay (942 nM)[1].

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

In Vivo

Gandotinib (LY2784544) effectively inhibits STAT5 phosphorylation in Ba/F3-JAK2V617F-GFP (green fluorescent protein) ascitic tumor cells (TED_{50}=12.7 mg/kg) and significantly reduces (P<0.05) Ba/F3-JAK2V617F-GFP tumor burden in the JAK2V617F-induced MPN model (TED_{50}=13.7 mg/kg, twice daily)[1].

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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) (1×10^4 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 IC_{50} 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 (1×10^7) 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.

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