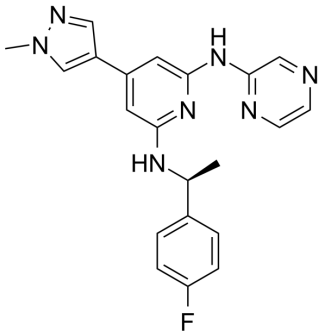
Ilginatinib



Cat. No.:	HY-19631A
CAS No.:	1239358-86-1
Molecular Formula:	$C_{21}H_{20}FN_7$
Molecular Weight:	389.43
Target:	JAK
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 : 100 mg/mL (256.79 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5679 mL	12.8393 mL	25.6786 mL
	5 mM	0.5136 mL	2.5679 mL	5.1357 mL
	10 mM	0.2568 mL	1.2839 mL	2.5679 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 (6.42 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.42 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.42 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ilginatinib (NS-018) is a highly active and orally bioavailable JAK2 inhibitor, with an IC_{50} of 0.72 nM, 46-, 54-, and 31-fold selectivity for JAK2 over JAK1 (IC_{50}, 33 nM), JAK3 (IC_{50}, 39 nM), and Tyk2 (IC_{50}, 22 nM).

IC_{50} & Target				
	JAK2 0.72 nM (IC_{50})	Tyk2 22 nM (IC_{50})	JAK1 33 nM (IC_{50})	JAK3 39 nM (IC_{50})

In Vitro

Ilginatinib (NS-018) is a highly active JAK2 inhibitor, with an IC_{50} of 0.72 nM, 46-, 54-, and 31-fold selectivity for JAK2 over

	JAK1 (IC_{50}, 33 nM), JAK3 (IC_{50}, 39 nM), and Tyk2 (IC_{50}, 22 nM). Ilginatinib (NS-018) also inhibits Src-family kinases, especially SRC and FYN, and weakly inhibits ABL and FLT3 with 45- and 90-fold selectivity for JAK2, respectively. NS-018 shows potent inhibitory activity against cell lines JAK2V617F or MPLW515L mutations or the TEL-JAK2 fusion gene (expressing a constitutively activated JAK2) with IC_{50} of 11-120 nM, but has only minimal cytotoxicity against most other hematopoietic cell lines that have no constitutively activated JAK2[1]. Ilginatinib (NS-018) (0.5 μM) preferentially suppresses colony-forming unitgranulocyte/macrophage (CFU-GM) formation from myelodysplastic syndrome (MDS)-derived bone marrow mononuclear cells (BMMNCs). Ilginatinib (NS-018) (1 μM) suppresses the phosphorylation of STAT3 (the downstream kinase of JAK2) in CFU-GM-forming cells from MDS patients[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Ilginatinib (NS-018) (12.5, 25, 50, 100 mg/kg, p.o.) potently prolongs the survival of mice and reduces splenomegaly in a mouse Ba/F3-JAK2V617F disease model[1]. Ilginatinib (NS-018) (25, 50 mg/kg, p.o.) significantly reduces leukocytosis, hepatosplenomegaly and extramedullary hematopoiesis, improves nutritional status, and prolongs survival in JAK2V617F transgenic mice MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Bone marrow mononuclear cells (BMMNCs) from healthy volunteers and myelodysplastic syndrome (MDS) patients are incubated in MethoCult GF H4434 methylcellulose medium containing various hematopoietic cytokines at 1.0×10^5 cells/mL with or without Ilginatinib (NS-018) at 37°C in a humidified atmosphere of 5% CO_2. Commercially available purified normal human CD34-positive ($CD34^+$) BM cells are used as a control. Burst-forming unit-erythroid (BFU-E) and colonyforming unit-granulocyte/macrophage (CFU-GM) colonies are counted under an inverted microscope on day 14 of culture[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female BALB/c nude mice are placed in blanket cages in an environment maintained at 21-25°C and 45-65% relative humidity, with artificial illumination for 12 h and a ventilation frequency of at least 15 times/h. They are allowed free access to food pellets and tap water. Ba/F3-JAK2V617F cells (10^6 per mouse) are inoculated intravenously into 7-week-old mice. Administration of vehicle (0.5% methylcellulose) or Ilginatinib (NS-018) twice daily by oral gavage begins the day after cell inoculation. Survival is monitored daily, and moribund mice are humanely killed and their time of death is recorded for purposes of survival analysis. In a parallel study, all mice are humanely killed after 8 days of administration, and their spleens are removed and weighed[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Nakaya Y, et al. Efficacy of NS-018, a potent and selective JAK2/Src inhibitor, in primary cells and mouse models of myeloproliferative neoplasms. Blood Cancer J. 2011 Jul;1(7):e29.

[2]. Kuroda J, et al. NS-018, a selective JAK2 inhibitor, preferentially inhibits CFU-GM colony formation by bone marrow mononuclear cells from high-risk myelodysplastic syndrome patients. Leuk Res. 2014 May;38(5):619-24.

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