JAK3-IN-1

Cat. No.: HY-19544

CAS No.: 1805787-93-2

Molecular Formula: $C_{26}H_{30}ClN_7O_2$

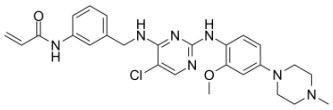
Molecular Weight: 508.02

Target: JAK

Pathway: Epigenetics; JAK/STAT Signaling; Stem Cell/Wnt

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (196.84 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9684 mL	9.8421 mL	19.6843 mL
5 mM	0.3937 mL	1.9684 mL	3.9369 mL
10 mM	0.1968 mL	0.9842 mL	1.9684 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 (4.92 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (4.92 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.92 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

JAK3-IN-1 is a potent, selective and orally active JAK3 inhibitor with an IC_{50} of 4.8 nM. JAK3-IN-1 shows over 180-fold more selective for JAK3 than JAK1 (IC_{50} of 896 nM) and JAK2 (IC_{50} of 1050 nM)[1].

IC_{50} & Target

JAK3 4.8 nM (IC_{50})	JAK1 896 nM (IC_{50})	JAK2 1050 nM (IC_{50})	TTK 49 nM (IC_{50})
BTK 794 nM (IC_{50})	ITK 1070 nM (IC_{50})		

In Vitro

JAK3-IN-1(Compound 9; 0-5 μM; 3 hours; BMDMs cells) treatment completely inhibits IL-4 induced p-STAT6 at a concentration of 500 nM and only partially inhibits IFNβ-induced p-STAT1 at a concentration of 5.0 μM[1].

.JAK3-IN-1(Compound 9) most potently inhibits JAK3 and identified fms-related tyrosine kinase 3 (FLT3) and several tyrosine protein kinase (TEC)-family kinases as being potential off-targets. Enzymatic assays using the Z'-lyte or LanthaScreen formats confirmed enzymatic inhibition of FLT3 (IC_{50} = 13 nM), TTK protein kinase (TTK, IC_{50} = 49 nM), BLK proto-oncogene (BLK, IC_{50} = 157 nM) and tyrosine protein kinase TXK (TXK, IC_{50} = 36 nM). JAK3-IN-1 shows very low inhibition scores for other JAKs and wild-type (WT) EGFR, which is consistent with the over 180-fold higher IC_{50}s against EGFRWT and TYK2 (IC_{50}s =409 nM, > 10000 respectively). JAK3-IN-1 possesses over 165-fold higher IC_{50}s for BTK or ITK (IC_{50}s = 794 and 1070 nM respectively)[1].

JAK3-IN-1(Compound 9) selectively inhibits the proliferation of JAK3-dependent Ba/F3 cells (IC_{50} = 69 nM) relative to other JAK-dependent Ba/F3 cells, for which there was no antiproliferative effect at concentrations below 3.0 μM[1].

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

Western Blot Analysis[1]

Cell Line:	BMDMs cells
Concentration:	0 μM, 0.1 μM, 0.5 μM, 1 μM, 5 μM
Incubation Time:	3 hours
Result:	Completely inhibited IL-4 induced p-STAT6 at a concentration of 500 nM and only partially inhibited IFNβ-induced p-STAT1 at a concentration of 5.0 μM.

In Vivo

JAK3-IN-1(Compound 9) shows reasonable pharmacokinetic properties, with moderate $T_{1/2}$ of 1.4 h, area under the curve (AUC) value of 795 ng*hr/mL following a 10 mg/Kg oral dose and good oral bioavailability of 66%. After oral administration with JAK3-IN-1(Compound 9) (75 mpk, QD) for 8 days, the numbers of B or T lymphocytes in the tumor-bearing lungs and spleens of treated mice is not affected, however, the number of NK cells is reduced[1].

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

REFERENCES

[1]. Tan L, et al. Development of Selective Covalent Janus Kinase 3 Inhibitors. J Med Chem. 2015 Aug 27;58(16):6589-6606.

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