Ritlecitinib

Cat. No.: HY-100754

CAS No.: 1792180-81-4

Molecular Formula: $C_{15}H_{19}N_5O$

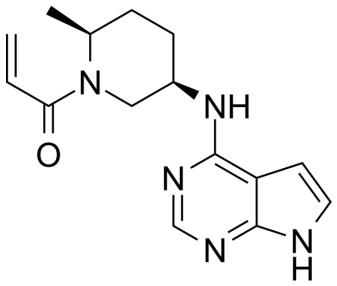
Molecular Weight: 285.34

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 : 125 mg/mL (438.07 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	3.5046 mL	17.5230 mL	35.0459 mL
	5 mM	0.7009 mL	3.5046 mL	7.0092 mL
	10 mM	0.3505 mL	1.7523 mL	3.5046 mL

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

In Vivo

1. Add each solvent one by one: 0.5% MC >> 0.5% Tween-80
   Solubility: 6.67 mg/mL (23.38 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (7.29 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (7.29 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (7.29 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ritlecitinib (PF-06651600) is an orally active and selective JAK3 inhibitor with an IC_{50} of 33.1 nM[1].

IC_{50} & Target

JAK3
33.1 nM (IC_{50})

In Vitro	Ritlecitinib is a potent JAK3-selective inhibitor which can inhibit the JAK3 kinase activity with an IC_{50} of 33.1 nM but without activity (IC_{50}>10 000 nM) against JAK1, JAK2, and TYK2. Ritlecitinib inhibits the phosphorylation of STAT5 elicited by IL-2, IL-4, IL-7, and IL-15 with IC_{50} values of 244, 340, 407, and 266 nM, respectively. Ritlecitinib also inhibits the phosphorylation of STAT3 elicited by IL-21 with an IC_{50} of 355 nM. Functional assessment in T-cell differentiation assays demonstrate that Ritlecitinib suppresses Th1 and Th17 differentiation as measured by IFNγ, after 5 days under Th1 conditions, and IL-17 production, after 6 days under Th17 conditions, with IC_{50} values of 30 nM and 167 nM, respectively. Ritlecitinib also suppresses Th1 and Th17 function as measured by the inhibition of IFNγ production (IC_{50}=48 nM) and IL-17 production (IC_{50} =269 nM) in cells that have been previously differentiated and rested before being treated with PF-06651600[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In the rat adjuvant-induced arthritis (AIA) model, Ritlecitinib reduces paw swelling with an unbound EC_{50} of 169 nM. Similarly, Ritlecitinib significantly reduces disease severity in the experimental autoimmune encephalomyelitis (EAE) mouse model when dosed either therapeutically at 30 or 100 mg/kg or prophylactically at 20 and 60 mg/kg. The efficacy of Ritlecitinib in these two rodent models of inflammatory and autoimmune diseases illustrates that JAK3-selective inhibition can be sufficient to have disease modifying effects in human diseases[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	To study the effect of PF-06651600 on Th17 cells post differentiation, skewed Th17 cells are washed, rested with medium for overnight and resuspended in medium containing the same concentrations of cytokines as during skewing but without anti-CD3 or anti-CD28 antibodies, in the presence of PF-06651600 at 10 different concentrations for 2 additional days. On Day 9, supernatant is harvested from each well and IL-17A is determined[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	The effect of JAK3 inhibition by PF-06651600 is evaluated in vivo using a therapeutic dosing paradigm in a rat adjuvant-induced arthritis. When individual hind paw volume measurements indicate an increase of 0.2 mL (or greater) in a single hind paw, animals are randomly assigned to a treatment group. Daily treatment with PF-06651600 is administered via oral gavage. Treatment groups for Experiment 1 are: 80, 15, or 6 mg/kg of PF-06651600 or vehicle (2% Tween 80/0.5% methylcellulose/deionized water). Treatment groups for Experiment 2 are: 30, 10, and 3 mg/kg of PF-06651600 or vehicle (0.5% methylcellulose/de-ionized water/1 mEQ hydrochloric acid). Treatment groups for Experiment 3 are: 10, 1, 0.3 and 0.1 mg/kg of PF-06651600 or vehicle (0.5% methylcellulose/de-ionized water/1 mEQ hydrochloric acid). Treatment continues for 7 days[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Blood Adv. 2022 May 23;bloodadvances.2022007695.
- Expert Opin Investig Drugs. 2021 Nov 26.
- Int J Mol Sci. 2023 May 25, 24(11), 9243.
- Inflamm Bowel Dis. 2020 Dec 9;izaa318.
- bioRxiv. 2023 Aug 17.

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REFERENCES

[1]. Telliez JB, et al. Discovery of a JAK3-Selective Inhibitor: Functional Differentiation of JAK3-Selective Inhibition over pan-JAK or JAK1-Selective Inhibition. ACS Chem Biol. 2016 Dec 16;11(12):3442-3451.

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