CHZ868

Cat. No.: HY-18960

CAS No.: 1895895-38-1

Molecular Formula: $C_{22}H_{19}F_2N_5O_2$

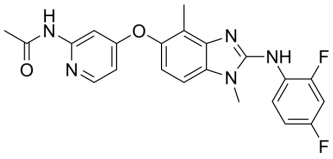
Molecular Weight: 423.42

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	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (236.17 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3617 mL	11.8086 mL	23.6172 mL
	5 mM	0.4723 mL	2.3617 mL	4.7234 mL
	10 mM	0.2362 mL	1.1809 mL	2.3617 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 (5.90 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.90 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.90 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CHZ868 is a type II JAK2 inhibitor with an IC_{50} of 0.17 μM in EPOR JAK2 WT Ba/F3 cell.

IC_{50} & Target

JAK2
110 nM (IC_{50})

In Vitro

CHZ868 potently inhibits constitutive JAK2 and STAT5 phosphorylation in JAK2V617F SET2 cells. CHZ868 potently inhibits the proliferation of SET2 cells (GI_{50}=59nM), and has 6-fold less growth inhibitory activity against CMK cells (GI_{50}=378nM)[1].

	At 100 nM CHZ868 has activity against 26 kinases, including JAK2 and TYK2. CHZ868 is thought to engage with the hinge region of JAK2 through two H-bonds, formed between the amino-pyridine of CHZ868 and the backbone-NH/CO of L932, while the pyridine is occupying the adenine pocket of the ATP binding site. CHZ868 potently suppresses the growth of CRLF2-rearranged human B-ALL cells, abrogates JAK2 signaling[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CHZ868 is characterized by high passive permeability, good metabolic stability, and low water solubility, as well as by moderate blood clearance and good oral bioavailability, making it suitable for in vivo use. CHZ868 improves survival in mice with human or murine B-ALL. CHZ868 and dexamethasone synergistically induces apoptosis in JAK2-dependent B-ALLs and further improves survival compared to CHZ868 alone[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	CHZ868 is dissolved in DMSO to make 10 mM stock solution and diluted in culture media. Cells are treated with CHZ868 (0, 0.05, 0.1, 0.2 μM) or vehicle (DMSO). After 48 hr (Ba/F3 cells) or 72 hr (MHH-CALL4 and PDX cells), CellTiter-Glo Luminescent Cell Viability Assay is added (10 μL undiluted or 25 μL of a 1:2 dilution in each well) and plates are read[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice: CHZ868 is reconstituted in 0.5% methylcellulose / 0.5% Tween-80 and administered at doses of 10 or 30 mg/kg/day by oral gavage. Pharmacokinetic/pharmacodynamic and efficacy studies in the mouse model of rhEpo-induced polycythemia are carried out essentially as reported. Detection of STAT5 phosphorylation in spleen lysates by Meso Scale Discovery is performed[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Commun. 2021 Jun 15;12(1):3651.
- Leukemia. 2019 Jun;33(6):1373-1386.
- NPJ Precis Oncol. 2021 Aug 10;5(1):75.
- Biomed Pharmacother. 2018 Mar;99:278-285.
- Hemasphere. 2021 Aug 11;5(9):e630.

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REFERENCES

[1]. Meyer SC, et al. CHZ868, a Type II JAK2 Inhibitor, Reverses Type I JAK Inhibitor Persistence and Demonstrates Efficacy in Myeloproliferative Neoplasms. Cancer Cell. 2015 Jul 13;28(1):15-28.

[2]. Wu SC, et al. Activity of the Type II JAK2 Inhibitor CHZ868 in B Cell Acute Lymphoblastic Leukemia. Cancer Cell. 2015 Jul 13;28(1):29-41.

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