

Product Data Sheet

Product Name: CHZ868
Cat. No.: GC11652

Chemical Properties

Cas. No. 1895895-38-1

Chemical Name N-(4-((2-((2,4-difluorophenyl)amino)-1,4-dimethyl-1H-benzo[d]imidazol-5-yl)oxy)pyridin-2-yl)acetamide

SMILES CN(C(NC1=CC=C(F)C=C1F)=N2)C(C2=C3C)=CC=C3OC4=CC=NC(NC(C)=O)=C4

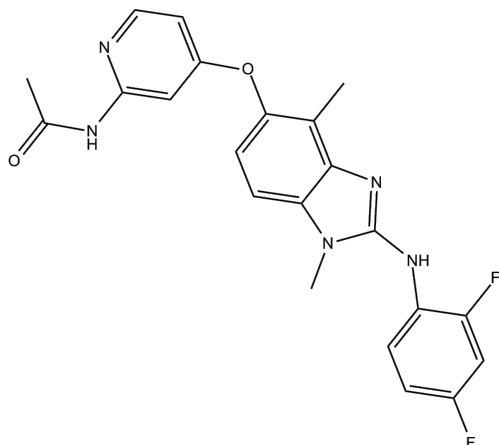
Formula C22H19F2N5O2 M.Wt 423.42

Solubility Soluble in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

Caution: Product has not been fully validated for medical applications. For research use only.

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Cell lines	CRLF2-rearranged human B-ALL cells MHH-CALL4, JAK2V617F SET2 cells, MPLW515L mutant cells
Preparation method	Soluble in DMSO. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.
Reacting condition	0.25-1 µM
Applications	In CRLF2-rearranged human B-ALL cells MHH-CALL4, CHZ868 potently inhibited JAK2 phosphorylation and cell growth. In JAK2V617F SET2 cells, CHZ868 (0.25-1 µM) potently inhibited constitutive JAK2 and STAT5 phosphorylation, and inhibited cell proliferation with GI50 of 59 nM. In MPLW515L mutant cells, CHZ868 potently inhibited cell proliferation and abrogated phosphorylation of Y1007/Y1008 in the JAK2 activation loop. In type I JAK inhibitor-persistent cells, CHZ868 dose-dependently inhibited JAK2 phosphorylation and proliferation of JAK2V617F or MPLW515L cells.
Animal experiment [1]:	
Animal models	Jak2V617F conditional knock-in mice
Dosage form	30-40 mg/kg orally once daily

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Application

CHZ868 normalized spleen and liver weights, demonstrating marked inhibition of extramedullary hematopoiesis. CHZ868 therapy reduced the bone marrow megakaryocytic hyperplasia. In a murine model of PMF-like disease, CHZ868 (40 mg/kg) therapy significantly improved survival of mice with MPLW515L-induced myelofibrosis and dose-dependently reduced hepatomegaly and normalized spleen weight and size. CHZ868 therapy markedly decreased bone marrow and spleen reticulin fibrosis.

Other notes

Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1]. Meyer S C, Keller M D, Chiu S, et al. CHZ868, a type II JAK2 inhibitor, reverses type I JAK inhibitor persistence and demonstrates efficacy in myeloproliferative neoplasms[J]. Cancer cell, 2015, 28(1): 15-28.

Background

CHZ868 is a type II JAK2 inhibitor with IC₅₀ value of 110 nM [1].

JAK2 (Janus kinase 2) is a non-receptor tyrosine kinase. Mutations in JAK2 is associated with many myeloproliferative disorders.

In CRLF2-rearranged human B-ALL cells MHH-CALL4, CHZ868 potently inhibited JAK2 phosphorylation and cell growth [1]. CHZ868 is a type II JAK2 inhibitor. In JAK2V617F SET2 cells, CHZ868 potently inhibited constitutive JAK2 and STAT5 phosphorylation, and inhibited cell proliferation with GI₅₀ value of 59 nM. In MPLW515L mutant cells, CHZ868 potently inhibited cell proliferation and abrogated phosphorylation of Y1007/Y1008 in the JAK2 activation loop. In type I JAK inhibitor-persistent cells, CHZ868 potently and concentration-dependently inhibited JAK2 phosphorylation and proliferation of JAK2V617F or MPLW515L cells [2].

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In mice with human or murine B-ALL, CHZ868 improved survival. In JAK2-dependent B-ALL mice, CHZ868 and dexamethasone synergistically induced apoptosis and improved survival compared to CHZ868 alone [1]. In Jak2V617F-driven polycythemia vera (PV), CHZ868 (30 - 40 mg/kg orally once daily) inhibited JAK-STAT signaling and significantly reduced the proportion of mutant cells in the bone marrow. In MPLW515L-induced myelofibrosis (MF), CHZ868 completely inhibited STAT3 and STAT5 phosphorylation, and reduced JAK2 phosphorylation. CHZ868 also improved survival and reduced hepatomegaly in a dose-dependent way [2].

References:

- [1]. Wu SC, Li LS, Kopp N, et al. Activity of the Type II JAK2 Inhibitor CHZ868 in B Cell Acute Lymphoblastic Leukemia. *Cancer Cell*, 2015, 28(1): 29-41.
- [2]. Meyer SC, Keller MD, Chiu S, et al. CHZ868, a Type II JAK2 Inhibitor, Reverses Type I JAK Inhibitor Persistence and Demonstrates Efficacy in Myeloproliferative Neoplasms. *Cancer Cell*, 2015, 28(1): 15-28.

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