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PIM-447 dihydrochloride

Cat. No.: HY-19322B

CAS No.: 1820565-69-2

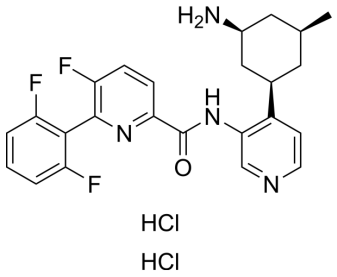
Molecular Formula: $C_{24}H_{25}Cl_2F_3N_4O$

Molecular Weight: 513.38

Target: Pim; Apoptosis

Pathway: JAK/STAT Signaling; Apoptosis

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 1 year; -20°C, 6 months (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

H_2O : 50 mg/mL (97.39 mM; Need ultrasonic)
DMSO : ≥ 46.7 mg/mL (90.97 mM)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9479 mL	9.7394 mL	19.4787 mL
5 mM	0.3896 mL	1.9479 mL	3.8957 mL
10 mM	0.1948 mL	0.9739 mL	1.9479 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 (4.87 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PIM447 dihydrochloride (LGH447 dihydrochloride) is a potent, orally available, and selective pan-PIM kinase inhibitor, with K_i values of 6, 18, and 9 pM for PIM1, PIM2, and PIM3, respectively. PIM447 dihydrochloride displays dual antimyeloma and bone-protective effects. PIM447 dihydrochloride induces apoptosis[1][2].

IC_{50} & Target	PIM1	PIM2	PIM3

In Vitro

PIM-447?(0.05-10 μM; 24, 48 and 72 hours) has inhibitory effects in MM cells, it against sensitive cell lines with IC_{50} values ranging from 0.2 to 3.3 μM (MM1S, MM1R, RPMI-8226, MM144, U266 and NCI-H929) and less sensitive cell lines with IC_{50} values at 48 h >7 μM (OPM-2, RPMI-LR5, U266-Dox4 and U266-LR7)[1].

PIM-447?(0.1-10 μM; 24, 48 and 72 hours) does not induce important levels of apoptosis, when PIM447 at 5 μM, it substantially increases annexin-V levels (about 30%) in sensitive cell lines(MM1S, NCI-H929 and RPMI-8226). When PIM447 at 10 μM, it induces apoptosis in all the cell lines but to a lesser extent in OPM-2 and RPMI-LR5[1].
PIM447 promotes the cleavage of initiator caspases, such as caspases 8 and 9, and increases the cleavage of the effector caspases 3 and 7, together with PARP cleavage in MM1S,RPMI-8226 and NCI-H929 cells[1].
PIM447 (0.1-1 μM) increases the percentage of cells in the G0/G1 phase and decreases the proliferative phases (S and G2/M) of the cell cycle. The effects at low concentrations (0.1-1 μM) were more pronounced in MM1S cells than in OPM-2[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	Sensitive MM cell lines: MM1S, MM1R, RPMI-8226, MM144, U266 and NCI-H929 cells Less sensitive MM cell lines: OPM-2,RPMI-LR5, U266-Dox4 and U266-LR7cells
Concentration:	0.05-10 μM
Incubation Time:	24, 48 and 72 hours
Result:	Was cytotoxic for MM cells (PIM kinases highly expressed).

Apoptosis Analysis[1]

Cell Line:	Sensitive MM cell lines: MM1S, NCI-H929 and RPMI-8226 cells Less sensitive MM cell lines: OPM-2 and RPMI-LR5 cells
Concentration:	0.05-10 μM
Incubation Time:	24, 48 and 72 hours
Result:	Induced cell apoptosis at higer doses, had no effects at 0.1-1 uM.

Western Blot Analysis[1]

Cell Line:	Sensitive MM cell lines: MM1S, NCI-H929 and RPMI-8226 cells
Concentration:	0.05-10 μM
Incubation Time:	24, 48 hours
Result:	Increased the cleavage of the effector caspases 3 and 7, and the PARP cleavage.

Cell Cycle Analysis[1]

Cell Line:	MM1S, OPM-2 cells
Concentration:	0.1, 0.5 or 1 μM
Incubation Time:	48 hours
Result:	Increased the cleavage of the effector caspases 3 and 7, and the PARP cleavage.

In Vivo

PIM447 (oral gavage; 100 mg/kg; 5 times/week) clearly controlls tumor progression and the serum levels of hIgλ secreted by RPMI-8226-luc cells in mouse model of bone marrow-disseminated human multiple myeloma[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	RPMI-8226-luc cells are injected intravenously into 6-week-old female NODSCID-IL-2Rγ$^{-/-}$ (NSG) mice[1]

Dosage:	100 mg/kg
Administration:	oral gavage; 100 mg/kg; 5 times/week
Result:	Was well tolerated, as the body weight of mice did not decrease by more than 10%. Increased bone volume density and trabecular number and reduced trabecular separation relative to vehicle group.

CUSTOMER VALIDATION

- Cell Chem Biol. 2023 Nov 16:S2451-9456(23)00384-7.
- J Pathol. 2020 Sep;252(1):65-76.
- Mol Cancer Ther. 2018 Apr;17(4):849-857.

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REFERENCES

[1]. Paíno T et al. The novel pan-PIM kinase inhibitor, PIM447, displays dual anti-myeloma and bone protective effects, and potently synergizes with current standards of care. Clin Cancer Res. 2016 Jul 20.

[2]. Burger MT et al. Identification of N-(4-((1R,3S,5S)-3-Amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide (PIM447), a Potent and Selective Proviral Insertion Site of Moloney Murine Leukemia (PIM) 1, 2, and 3 Kinase Inhibitor in Clinical Trials for Hematological Malignancies. J Med Chem. 2015 Nov 12;58(21):8373-86.

[3]. Peters TL et al. Control of translational activation by PIM kinase in activated B-cell diffuse large B-cell lymphoma confers sensitivity to inhibition by PIM447.Oncotarget. 2016 Aug 20

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