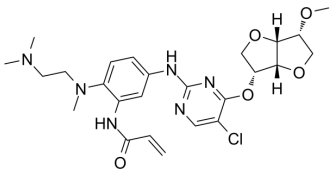
JAK3-IN-13

Cat. No.:	HY-150688
CAS No.:	2803329-86-2
Molecular Formula:	$C_{25}H_{33}ClN_6O_5$
Molecular Weight:	533.02
Target:	JNK
Pathway:	MAPK/ERK Pathway
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

JAK3-IN-13 is a potent, selective and orally active JAK3 inhibitor with IC_{50} values of 4728, 2039, 8, 365 nM for NK1, JNK2, JNK3, Tyk2, respectively. JAK3-IN-13 shows antiproliferative activity. JAK3-IN-13 induces cell cycle arrest at G0/G1 phase. JAK3-IN-13 shows antitumor activity[1].

IC_{50} & Target

JNK1	JNK2	JNK3	Tyk2
4728 nM (IC_{50})	2039 nM (IC_{50})	8 nM (IC_{50})	365 nM (IC_{50})

In Vitro

JAK3-IN-13 (compound 12n) (10 μM; 72 h) shows antiproliferative activity in BaF3-JAK3^{M511I}, U937, parental cells[1].
JAK3-IN-13 inhibits the activity of TEL-JNK1, TEL-JNK2, JNK3^{M511I}, JNK3 with IC_{50} values of 177.7, 134.2, 22.9, 1.2 nM, respectively[1].
JAK3-IN-13 inhibits (0-800 nM; 0-24 h) decreases the expression of phosphorylation JAK3, STAT3, and STAT5 in a dose-dependent manner[1].
JAK3-IN-13 inhibits (0-330 nM; 24 h) induces cell cycle arrest at G0/G1 phase and down-regulates the expression of cyclin-dependent kinase 2 (CDK2), CDK4, CDK6, cyclin B1, cyclin D3, and cyclin E1 in a concentration-dependent manner[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay[1]

Cell Line:	BaF3-JAK3^{M511I}, U937, parental, COLO-205, H1299, HCT-116, MDA-MB-231, AGS, HL 7702 cells
Concentration:	10 μM
Incubation Time:	72 h
Result:	Showed antiproliferative activity with IC_{50}s of 22.9, 20.2, 165.1 nM for BaF3-JAK3^{M511I}, U937, parental cells, and >10, >10, >10, >10, >10, 3.27 μM for COLO-205, H1299, HCT-116, MDA-MB-231, AGS, HL 7702 cells, respectively.

Western Blot Analysis[1]

Cell Line:	U937 cells
Concentration:	0-800 nM

Incubation Time:	0-24 h
Result:	Dose-dependently suppressed the phosphorylation of JAK3, STAT3, and STAT5 and achieved near-complete inhibition at 200 nM.

Cell Cycle Analysis[1]

Cell Line:	U937 cells
Concentration:	0-330 nM
Incubation Time:	24 h
Result:	Induced cell cycle arrest at G0/G1 phase and down-regulated the expression of cyclin-dependent kinase 2 (CDK2), CDK4, CDK6, cyclin B1, cyclin D3, and cyclin E1 in a concentration-dependent manner.

In Vivo

JAK3-IN-13 (5 mg/kg for i.v.; 15 mg/kg for p.o.) shows good PK properties and oral bioavailability of 20.66%[1].
JAK3-IN-13 (12.5, 25, 50 mg/kg; p.o.; twice daily for 10 days) shows antitumor activity and inhibits the expression of phosphorylation JAK3, STAT3, STAT5, CDK2, CDK4, CDK6, cyclin B1, cyclin D3, and cyclin E1[1].Pharmacokinetic Parameters of JAK3-IN-13 in Male Sprague-Dawley rats[1].

12n	i.v.(5 mg/kg)	p.o.(15 mg/kg)
anminal no.	3	3
$T_{1/2}$ (h)	0.91	0.98
C_{max} (ng/mL)	911.33	238.28
$AUC_{(0-\infty)}$ (h·ng/mL)	536.99	333.50
CL (mL/min/kg)	155.22	
F %		20.66

Male Sprague-Dawley rats, 5 mg/kg iv (5% DMSO + 10% solutol + 85% saline); 15 mg/kg po (0.5% HPMC in water)[1]
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male Sprague-Dawley rats[1]
Dosage:	5 mg/kg for i.v.; 15 mg/kg for p.o.
Administration:	I.v. or p.o.
Result:	Showed good PK properties and oral bioavailability of 20.66%.

Animal Model:	Male CB17-SCID mice (U937 mouse xenograft model)[1]
Dosage:	12.5, 25, 50 mg/kg
Administration:	P.o.; twice daily for 10 days (10 mg/kg; i.p.; once daily)

Result:	Dose-dependently inhibited the growth of the U937 tumor and significantly inhibited the expression of phosphorylation JAK3, STAT3, and STAT5 as well as the cell cycle-related proteins.

REFERENCES

[1]. Li S, et al. Discovery of Hexahydrofuro[3,2-b]furans as New Kinase-Selective and Orally Bioavailable JAK3 Inhibitors for the Treatment of Leukemia Harboring a JAK3 Activating Mutant. J Med Chem. 2022 Jul 20.

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