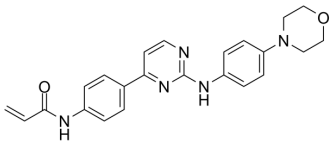
JAK3-IN-11

Cat. No.:	HY-146727
CAS No.:	2412734-00-8
Molecular Formula:	$C_{23}H_{23}N_5O_2$
Molecular Weight:	401.46
Target:	JAK
Pathway:	Epigenetics; JAK/STAT Signaling; Stem Cell/Wnt
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

JAK3-IN-11 (Compound 12), a potent, noncytotoxic, irreversible, orally active JAK3 inhibitor with IC_{50} value of 1.7 nM, has excellent selectivity (>588-fold compared to other JAK isoforms), covalently bind to the ATP-binding pocket in JAK3. JAK3-IN-11 strongly inhibits JAK3-dependent signaling and T cell proliferation, is a promising tool for study autoimmune diseases [1].

IC_{50} & Target

JAK3	JAK2	JAK1
1.7 nM (IC_{50})	1 μM (IC_{50})	1.32 μM (IC_{50})

In Vitro

JAK3-IN-11 (Compound 12) (10 μM, 72 h) has no obvious cytotoxicity at a concentration of 10 μM[1].
JAK3-IN-11 (Compound 12) (72 h) displays strong inhibition for T cell proliferation with IC_{50} values of 0.83 μM (anti-CD3/CD28 stimulation) and 0.77 μM (IL-2 stimulation)[1].
JAK3-IN-11 (Compound 12) (0-10 μM, 1h) abrogates IL-2 or IL-15-induced phosphorylation of STAT5 in a concentration-dependent manner[1].
JAK3-IN-11 (Compound 12) covalently binds to JAK3 and irreversibly inhibits JAK3[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay[1]

Cell Line:	Mouse T cells in complete RPMI1640 medium then exposed to anti-CD3/anti-CD28 or IL-2.
Concentration:	
Incubation Time:	72 h.
Result:	Displayed strong inhibition for T cell proliferation with an IC_{50} values of 0.83 μM (anti-CD3/CD28 stimulation) and 0.77 μM (IL-2 stimulation), showed obvious significant immunosuppressive activity under selective inhibition of JAK3.

Western Blot Analysis[1]

Cell Line:	Purified T cells were pre-activated coated with anti-CD3 and anti-CD28 for 72 h, then cultured with IL-2 (50 U/mL) for 36 h, then, cultured without IL-2 for 36 h
Concentration:	0.01, 0.1, 1, 10 μM.

Incubation Time:	1 h.
Result:	Abrogated IL-2 or IL-15-induced phosphorylation of STAT5 in a concentration-dependent manner.

In Vivo

JAK3-IN-11 (Compound 12) (Oxazolone (OXZ)-induced DTH Balb/c mice; 0-30 mg/kg; PO, prior to and during the challenge phase, 6 days) inhibits oxazolone (OXZ)-induced delayed type hypersensitivity (DTH) responses in a dose-dependent manner [1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Oxazolone (OXZ)-induced DTH Balb/c mice model[1].
Dosage:	30, 10, and 3 mg/kg.
Administration:	PO, prior to and during the challenge phase, 6 days.
Result:	Inhibited oxazolone (OXZ)-induced delayed type hypersensitivity (DTH) responses in a dose-dependent manner.

Animal Model:	Male ICR mice[1].
Dosage:	30 mg/kg for oral gavage, 10 mg/kg for intravenous administration.
Administration:	Pharmacokinetic Analysis
Result:	Preliminary pharmacokinetic data of JAK3-IN-11 (Compound 12) in male ICR Mice[1] Male ICR mice, 30 mg/kg for oral gavage, 10 mg/kg for intravenous administration[1].

Compound 12	iv (10 mg/kg)	po (30 mg/kg)
AUC(0-t) (mg/L*h)[a]	1244.41 ± 77.83	889.42 ± 48.32
AUC(0-∞) (mg/L*h)	1274.41 ± 57.18	897.12 ± 56.72
MRT (0-∞) (h)[b]	0.73 ± 0.08	1.42 ± 0.38
Vz (L/kg)[c]	8.36 ± 1.83	220.42 ± 24.71
CLz (L/h/kg)[d]	8.15 ± 1.21	97.14 ± 20.87
$t_{1/2}$ (h)[e]	0.47 ± 0.06	1.52 ± 0.34
C_{max} (mg/L)[f]	8763.23 ± 324.65	2008.21 ± 189.44
Bioavailability(%)[g]		23.82%

a Area under the concentration time curve.
b Mean residence time.
c Volume in steady state.
d Plasma clearance.

	e Terminal half-life. f Peak plasma concentrations. g Bioavailability = AUC_{0-t}(po)/AUC_{0-t} × 100%.

REFERENCES

[1]. Lei Shu, et al. Design, synthesis, and pharmacological evaluation of 4- or 6-phenyl-pyrimidine derivatives as novel and selective Janus kinase 3 inhibitors. Eur J Med Chem. 2020 Apr 1;191:112148.

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