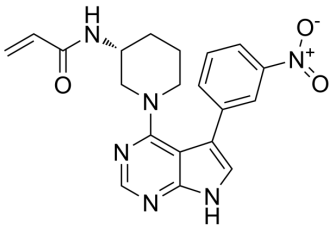
JAK3 covalent inhibitor-2

Cat. No.:	HY-161354
CAS No.:	2664050-97-7
Molecular Formula:	$C_{20}H_{20}N_6O_3$
Molecular Weight:	392.41
Target:	JAK; Apoptosis
Pathway:	Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt; Apoptosis
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	JAK3 covalent inhibitor-2 (compound J1b) is a selective, orally potent JAK3 inhibitor (IC_{50}=7.2 nM) with low toxicity, anti-inflammatory activity and good bioavailability[1].
IC_{50} & Target	JAK3 7.2 nM (IC_{50})
In Vitro	JAK3 covalent inhibitor-2 shows low cytotoxicity among HEK293, LO2, chondrocytes and RAW264.7 with IC_{50}s (72 h) of 86.82 μM (HEK293), 61.79 μM (LO2), >32 μM (chondrocytes) and >32 μM (RAW264.7) respectively[1]. JAK3 covalent inhibitor-2 (100 mM; 90 min) shows $t_{1/2}$ of 13.1 min and 43.9 min in human and rat liver microsomes, respectively. And the clean rate of 132.5 mL/min/kg and mL/min/kg, resepectively[1]. JAK3 covalent inhibitor-2 ((0.125-8 μM; 48 h)) dose-dependently induces T lymphocytes apoptosis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Apoptosis Analysis[1]

Cell Line:	$CD4^+$ T cells , CD8[1] T cells
Concentration:	0.125, 0.5, 1, 2, 4, 8 μM
Incubation Time:	48 h
Result:	Dose-dependently led to apoptosis among $CD4^+$ and $CD8^+$ T cells

In Vivo

Anti-inflammatory activity: JAK3 covalent inhibitor-2 (30 mg/kg, p.o.; single dose) inhibited carrageenan-induced paw edema in ICR mice, with a rapid reduction in paw thickness in J1b-treated mice[1].
Toxicity: JAK3 covalent inhibitor-2 (2 g/kg, p.o.; single dose) Liver and kidney appeare to be similar to those of normal mice, no weight loss or other adverse effects are observed[1].
Pharmacokinetics: JAK3 covalent inhibitor-2 (5 mg/kg; p.o.), clearance (Cl) 7.37 l/h/kg, oral half-life ($t_{1/2}$ = 3.77 h), and bioavailability (F = 31.69%)[1].

Pharmacokinetic parameters of compound JAK3 covalent inhibitor-2 in SD rats[1]

JAK3 covalent inhibitor-2 ⊠SD⊠⊠⊠⊠⊠⊠⊠⊠⊠⊠⊠⊠⊠[1]

Route	Dose (mg/kg)	C_{max} (mg/L)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (mg/L·h)	V<, V/F (L/kg)	Cl, Cl/F (L/h/kg)	F (%)
i.v.	5	4497.32	0.08	2.63	2161.38	8.98 (V)	2.32V (Cl)	31.69
p.o.	5	501.8	0.25	3.77	684.87	39.89 (V/F)	7.37 (Cl/F)	/

Treatment of arthritis: JAK3 covalent inhibitor-2 (60 mg/kg , p.o. once a day) in CIA model almost complete restoration of normal joint status is achieved, and no significant weight changes or other adverse effects are observed[1].

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

Animal Model:	ICR mice [1]
Dosage:	30 mg/kg
Administration:	p.o.
Result:	Showed significant anti-inflammatory activity by oral administration.

Animal Model:	C57BL/6 mice[1]
Dosage:	2 g/kg
Administration:	p.o.
Result:	Inhibited tumor growth. Livers and kidneys appeared to be similar to those of normal mice. No weight loss or other adverse effects were observed.

Animal Model:	SD rats[1]
Dosage:	5 mg/kg
Administration:	p.o
Result:	JAK3 covalent inhibitor-2 had good intestinal absorption and oral bioavailability. Clearance rate (Cl) was 7.37 L/h/kg, oral half□life (t1/2 = 3.77 h), F = 31.69%

Animal Model:	CIA model mouse[1]
Dosage:	JAK3 covalent inhibitor-2 (30 mg/kg), JAK3 covalent inhibitor-2 (60 mg/kg,) Tofacitinib□ HY-40354□ (30 mg/kg)
Administration:	p.o.
Result:	JAK3 covalent inhibitor-2 group at 60 mg/kg histopathological analysis showed that the joint had returned to almost normal conditions.

REFERENCES

[1]. Hualiang Y et al. Design and synthesis of highly selective Janus kinase 3 covalent inhibitors for the treatment of rheumatoid arthritis ARCH PHARM. 2024 Feb e2300753

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