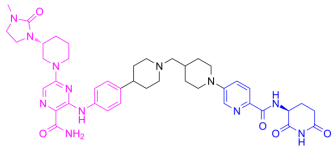
NX-5948

Cat. No.:	HY-153321
CAS No.:	2649400-34-8
Molecular Formula:	$C_{42}H_{54}N_{12}O_5$
Molecular Weight:	806.96
Target:	Btk; PROTACs
Pathway:	Protein Tyrosine Kinase/RTK; PROTAC
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (61.96 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.2392 mL	6.1961 mL	12.3922 mL
	5 mM	0.2478 mL	1.2392 mL	2.4784 mL
	10 mM	0.1239 mL	0.6196 mL	1.2392 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: ≥ 3.33 mg/mL (4.13 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 3.33 mg/mL (4.13 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3.33 mg/mL (4.13 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

NX-5948 (BTK-IN-24) is an orally active chimeric targeting molecule (CTM) that induces specific BTK protein degradation by the cereblon E3 ligase (CRBN) complex without degradation of other cereblon neo-substrates. NX-5948 mediates potent anti-inflammatory activity via BTK degradation with resultant inhibition of B cell activation. NX-5948 exhibits potent tumor growth inhibition in TMD8 xenograft models that contain either wild-type BTK or BTKi-resistant mutations. NX-5948 is efficacious in a mouse collageninduced arthritis (CIA) model. NX-5948 can cross the blood brain barrier (BBB). NX-5948 is a PROTAC composed of the ligand for target protein, a linker, and a cereblon E3 ligase (CRBN) complex (Red: ligand for target protein; Blue: CRBN; Black: linker)[1][2][3].

IC_{50} & Target	Cereblon
In Vitro	NX-5948 (BTK-IN-24; 0.0001-1000 nM; 4 h) is a potent degrader of BTK in primary human B cells (DC_{50}=0.34 nM) and inhibits BCR signaling[1]. NX-5948 induces the degradation of BTK (DC_{50}< 1 nM) in lymphoma cell lines and PBMCs[3]. NX-5948 (10 nM; 0.25, 0.5, 1, 2, 4, 6, 18, 24 h) catalyzes rapid BTK degradation within 1 hour and is complete within 2 hours in Ramos cells[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	NX-5948 (BTK-IN-24; 10, 30 mg/kg; po; daily; Day 18 to 36) is efficacious and well-tolerated in a mouse collagen-induced arthritis (CIA) model and suppresses antibody titers and IL-6 cytokine levels[1]. NX-5948 (3, 10, 30 mg/kg; po) causes dose- and time-dependent reduction in BTK levels in circulating murine and non-human primate, cynomolgus monkey B cells[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Mouse collagen-induced arthritis (CIA) model[1]
Dosage:	10, 30 mg/kg
Administration:	PO; daily; Day 18 to 36
Result:	Showed efficacious and well-tolerated in a mouse CIA model.

REFERENCES

[1]. Mark Noviski, et al. NX-5948, a Selective Degrader of BTK, Significantly Reduces Inflammation in a Model of Autoimmune Disease. 2021 Nurix Therapeutics, Inc.

[2]. 4473 Initial Findings from a First-in-Human Phase 1a/b Trial of NX-5948, a Selective Bruton's Tyrosine Kinase (BTK) Degrader, in Patients with Relapsed/Refractory B Cell Malignancies. Annual Meeting & Exposition, Monday, December 11, 2023.

[3]. Zi Liu, et al. An overview of PROTACs: a promising drug discovery paradigm. Mol Biomed. 2022 Dec 20;3(1):46.

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