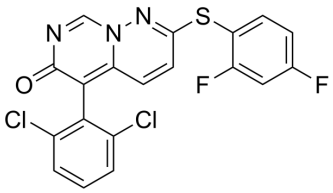
Neflamapimod

Cat. No.:	HY-10328
CAS No.:	209410-46-8
Molecular Formula:	$C_{19}H_9Cl_2F_2N_3OS$
Molecular Weight:	436
Target:	p38 MAPK; Autophagy
Pathway:	MAPK/ERK Pathway; Autophagy
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 : 13.08 mg/mL (30.00 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2936 mL	11.4679 mL	22.9358 mL
	5 mM	0.4587 mL	2.2936 mL	4.5872 mL
	10 mM	0.2294 mL	1.1468 mL	2.2936 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

Neflamapimod (VX-745) is a potent, blood-brain barrier penetrant, highly selective inhibitor of p38α inhibitor with an IC_{50} for p38α of 10 nM and for p38β of 220 nM. Neflamapimod (VX-745) possesses anti-inflammatory activity.

IC_{50} & Target

p38α	p38β
10 nM (IC_{50})	220 nM (IC_{50})

In Vitro

Neflamapimod (VX-745) exhibits PBMC IL-1β and TNFα IC_{50} values of 45 and 51 nM, respectively. Neflamapimod is also effective in whole blood, blocking IL-1β and TNFα release with IC_{50} values of 150 and 180 nM, respectively[1].
Neflamapimod shows a promising selectivity profile, with 20-fold selectivity for p38α over p38β (K_i=220 nM)[1].
Neflamapimod (VX-745) solutions in DMSO/DMEM inhibits the IL-6 production with IC_{50} of 15±9 nM[2].
Neflamapimod (VX-745; 5.0 nM) displays potent activity and 1000-fold selectivity over closely related kinases, including ERK1, JNK1-3 and MK2. Neflamapimod (10 nM-50 μM) increasingly inhibits the anisomycin-induced activity of p38α[3].
Neflamapimod (VX-745; 0.06 μM-20 μM) inhibits IL-6 and VEGF secretion in BMSCs. Neflamapimod can inhibit cytokine (TNF-α, IL-6, VEGF)-induced paracrine MM cell growth, survival, and drug resistance in the BM microenvironment. Neflamapimod induces modest growth inhibition of MM.1S, RPMI8226, and U266 cell lines in a dose-dependent fashion, with inhibitory

	concentration of 50% (IC_{50}) of 10 μM[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Neflamapimod (VX-745; 2.5, 5, and 10 mg/kg) improves the inflammatory scores in mice by 27%, 31%, and 44%, respectively [1]. Neflamapimod (VX-745; 1.06 mg/kg) significantly decreases the inflammation score from 2.07±0.29 for the control group to 1.42±0.06[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Neflamapimod inhibits p38α and p38β. The IC_{50} for the inhibition of these two p38 homologs are obtained by a spectrophotometric coupled-enzyme assay. A fixed concentration of enzyme (15 nM of p38α or p38β) is incubated with various concentrations of Neflamapimod in DMSO for 10 min. at 30°C in 0.1 M HEPES buffer, pH 7.5, containing 10% glycerol, 10 mM $MgCl_2$, 2.5 mM phosphoenolpyruvate, 200 μM NADH, 150 μg/mL pyruvate kinase, 50 μg/mL lactate dehydrogenase, and 200 μM EGF receptor peptide. The reaction is initiated with 100 μM and 70 μM ATP for p38α and p38β assays, respectively. The decrease of absorbance at 340 nm is monitored to follow the rate of the reaction. IC_{50} is evaluated from the rate data as a function of the inhibitor concentration. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	For these experiments, cells are plated at a density of 60,000 cells/well in 96-well plates. Each condition is tested in triplicate or more. The following day, all particle suspensions, active substances or control solutions are freshly prepared, distributed and incubated for 24 h at 37°C. Then, supernatants are carefully discarded. To perform the MTT test, 50 μL of 0.1% MTT solution is added to each well for 3 h. Each well is then incubated for 1 h with 200 μL of dimethyl sulfoxide. Absorbance is measured at 595 nm. Reported results are expressed as the means±SD. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Type II collagen-induced arthritis is established in male DBA/1 mice with a minor modification. 10-Week old male DBA/1 mice are immunized by two intradermal injections within a 3 week interval using 100 μL of an emulsion consisting of a 1:1 (v/v) mixture of chick type II collagen (200 μg in 10 mM acetic acid) and complete Freund's adjuvant. Following the booster immunization, the mice are left untreated for 2-3 weeks, and are randomized into five treatment groups after they exhibit focal carpal (wrist) swelling (level 2 arthritic severity score) in both front paws. The five treatment groups are: 1: water control, 10 mL/kg, p.o., bid, (n=14); 2: 100% propylene glycol (PG) vehicle control, 10 mL/kg, p.o., bid, (n=8); 3: Neflamapimod in PG, at 10 mg/kg, p.o., bid, (n=7); 4: Neflamapimod in PG, at 5 mg/kg, p.o., bid, (n=10); and 5: Neflamapimod in PG, at 2.5 mg/kg, p.o., bid, (n=11). Arthritic symptoms are scored every other day using a level 1 to level 5 scoring system. Paw inflammation begins with erythema at the wrist (level 1), progressing to focal swelling of the wrist (level 2), to complete swelling of the wrist (level 3), to complete swelling of wrist and palm (level 4), and finally to complete swelling of wrist, palm and fingers (level 5). The sums of the scores from both front paw scores are used for plotting disease progression curves. Mice are sacrificed on day 20 and paws are removed, sectioned sagitally, stained with hemotoxylin & eosin, and scored for inflammation. Histologically, wrist joint inflammation begins with an infiltration of the synovium into the joint space (level 1), progressing to joint cartilage erosion (level 2), to joint cartilage and bone erosion (level 3), and finally to erosion of cartilage and bone accompanied by pannus formation (level 4). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Nanotechnol. 2021 Jul;16(7):830-839.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Biochem Pharmacol. 2023 Jul 8;115683.

- bioRxiv. 2023 Jan 17.
- Research Square Preprint. 2022 May.

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[1]. Duffy JP, et al. The Discovery of VX-745: A Novel and Selective p38α Kinase Inhibitor. ACS Med Chem Lett. 2011 Jul 28;2(10):758-63.

[2]. Pradal J, et al. Intra-articular bioactivity of a p38 MAPK inhibitor and development of an extended-release system. Eur J Pharm Biopharm. 2015 Jun;93:110-7.

[3]. Bagley MC, et al. Rapid synthesis of VX-745: p38 MAP kinase inhibition in Werner syndrome cells. Bioorg Med Chem Lett. 2007 Sep 15;17(18):5107-10. Epub 2007 Jul 13.

[4]. Hideshima T, et al. Targeting p38 MAPK inhibits multiple myeloma cell growth in the bone marrow milieu. Blood, 2003, 101(2), 703-705.

[5]. Cicenas J, et al. JNK, p38, ERK, and SGK1 Inhibitors in Cancer. Cancers (Basel). 2017 Dec 21;10(1).

[6]. Alam JJ. Selective Brain-Targeted Antagonism of p38 MAPKα Reduces Hippocampal IL-1β Levels and Improves Morris Water Maze Performance in Aged Rats. J Alzheimers Dis. 2015;48(1):219-27.

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