

产品名称: **VX-745**  
 产品别名: **Neflamapimod**

生物活性:				
Description	Neflamapimod (VX-745) is a potent, blood-brain barrier penetrant, highly selective inhibitor of p38α inhibitor with an IC <sub>50</sub> for p38α of 10 nM and for p38β of 220 nM. Neflamapimod (VX-745) possesses anti-inflammatory activity.			
IC <sub>50</sub> & Target	p38α	p38β		
	10 nM (IC <sub>50</sub> )	220 nM (IC <sub>50</sub> )		
In Vitro	Neflamapimod (VX-745) exhibits PBMC IL-1β and TNFα IC50 values of 45 and 51 nM, respectively			
	Neflamapimod is also effective in whole blood, blocking IL-1β and TNFα release with IC50 values of 150 and 180 nM, respectively[1].			
	Neflamapimod shows a promising selectivity profile, with 20-fold selectivity for p38α over p38β (Ki=220 nM)[1].			
	Neflamapimod (VX-745) solutions in DMSO/DMEM inhibits the IL-6 production with IC50 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].			
In Vivo	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% (IC50) of 10 μM[4].			
	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].			
Solvent&Solubility	<b>In Vitro:</b>			
	<b>DMSO : 13.08 mg/mL (29.98 mM; Need ultrasonic)</b>			
	Preparing Stock Solutions	Solvent	Mass	
		Concentration		
		1 mM	2.2922 mL	11.4611 mL
5 mM	0.4584 mL	2.2922 mL	4.5844 mL	
10 mM	0.2292 mL	1.1461 mL	2.2922 mL	
*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液; 一旦配成溶液, 请分装保存, 避免反复冻融造成的产品失效。				
储备液的保存方式和期限 -80°C, 6 months; -20°C, 1 month。 -80°C 储存时, 请在 6 个月内使用, -20°C 储存时, 请在 1 个月内使用。				
References	[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]. Cicenias J, et al. JNK, p38, ERK, and SGK1 Inhibitors in Cancer. Cancers (Basel). 2017 Dec 21;10(1).			
	[3]. 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.			
	[4]. Alam JJ. Selective Brain-Targeted Antagonism of p38 MAPKα Reduces Hippocampal IL-1β Levels			

	<p>and Improves Morris Water Maze Performance in Aged Rats. <i>J Alzheimers Dis.</i> 2015;48(1):219-27.</p> <p>[5]. Bagley MC, et al. Rapid synthesis of VX-745: p38 MAP kinase inhibition in Werner syndrome cells. <i>Bioorg Med Chem Lett.</i> 2007 Sep 15;17(18):5107-10. Epub 2007 Jul 13.</p> <p>[6]. Hideshima T, et al. Targeting p38 MAPK inhibits multiple myeloma cell growth in the bone marrow milieu. <i>Blood</i>, 2003, 101(2), 703-705.</p>
<b>实验参考:</b>	
<b>Cell Assay</b>	<p>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. [2]</p>
<b>Animal Administration</b>	<p>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 sagittally, stained with hemotoxylin &amp; 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). [1]</p>
<b>Kinase Assay</b>	<p>Neflamapimod inhibits p38α and p38β. The IC<sub>50</sub> 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<sub>2</sub>, 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<sub>50</sub> is evaluated from the rate data as a function of the inhibitor concentration. [1]</p>
	<p>[1]. Duffy JP, et al. The Discovery of VX-745: A Novel and Selective p38α Kinase Inhibitor. <i>ACS Med Chem Lett.</i> 2011 Jul 28;2(10):758-63.</p> <p>[2]. Cienas J, et al. JNK, p38, ERK, and SGK1 Inhibitors in Cancer. <i>Cancers (Basel)</i>. 2017 Dec 21;10(1).</p>

<p><b>References</b></p>	<p>[3]. Pradal J, et al. Intra-articular bioactivity of a p38 MAPK inhibitor and development of an extended-release system. <u>Eur J Pharm Biopharm.</u> 2015 Jun;93:110-7.</p> <p>[4]. Alam JJ. Selective Brain-Targeted Antagonism of p38 MAPK<math>\alpha</math> Reduces Hippocampal IL-1<math>\beta</math> Levels and Improves Morris Water Maze Performance in Aged Rats. <u>J Alzheimers Dis.</u> 2015;48(1):219-27.</p> <p>[5]. Bagley MC, et al. Rapid synthesis of VX-745: p38 MAP kinase inhibition in Werner syndrome cells. <u>Bioorg Med Chem Lett.</u> 2007 Sep 15;17(18):5107-10. Epub 2007 Jul 13.</p> <p>[6]. Hideshima T, et al. Targeting p38 MAPK inhibits multiple myeloma cell growth in the bone marrow milieu. <u>Blood.</u> 2003, 101(2), 703-705.</p>
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源叶生物