产品名称：
N-(6-CHLORO-9H-PYRIDO[3,4-B]INDOL-8-YL)-3-PYRIDINECARBOXAMIDE DIHYDROCHLORIDE
产品别名：**PS-1145**

生物活性：

Description	PS-1145 is an IκB kinase (IKK) inhibitor with an IC_{50} of 88 nM.
IC_{50} & Target	IKK
	88 nM (IC_{50})
In Vitro	PS-1145 blocks TNFα-induced NF-κB activation in a dose- and time-dependent fashion in MM cells through inhibition of IκBα phosphorylation. Dexamethasone (Dex), which up-regulates IκBα protein, enhances blockade of NF-κB activation by PS-1145. PS-1145 blocks the protective effect of IL-6 against Dex-induced apotosis. TNFα-induced intracellular adhesion molecule (ICAM)-1 expression on both RPMI8226 and MM.1S cells is also inhibited by PS-1145. Moreover, PS-1145 inhibits both IL-6 secretion from bone marrow stromal cells (BMSCs) triggered by MM cell adhesion and proliferation of MM cells adherent to BMSCs[1].
In Vivo	Administration of either Bortezomib or PS-1145 (50 mg/kg) results in a significant decrease in serum levels of all 3 cytokines that is nonsignificantly different from those in mice that underwent transplantation with TCD BM alone[2]. PS1145 is injected intracerebroventricular (icv) as a pretreatment to block hypothalamic inflammation induced by IL-4 in adult male Wistar rats consuming a high-fat diet (HFD) over an 11-day period. The four groups of rats according to icv pretreatment/treatment condition are Veh/Veh, Veh/IL-4, PS1145/Veh, and PS1145/IL-4. Rats in the Veh/IL-4 group display increased weight gain on the HFD compared with the Veh/Veh group (P<0.05 on days 6-9). Importantly, the effect of icv IL-4 administration to increase body fat mass during high-fat (HF) feeding is completely blocked by icv PS1145 pretreatment at a dose that has no independent effect on body composition (on day 8: P<0.001, PS1145/Veh vs. PS1145/IL-4; P=not significant, PS1145/Veh vs. Veh/Veh). In PS1145/IL-4 injected rats, IL-1β mRNA content is decreased by ~75% compared with that of Veh/IL-4-injected rats[3].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 43 mg/mL** (**133.23 mM**) **H_2O : < 0.1 mg/mL** (insoluble) * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.0984 mL	15.4919 mL	30.9837 mL
5 mM	0.6197 mL	3.0984 mL	6.1967 mL
10 mM	0.3098 mL	1.5492 mL	3.0984 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。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现

	用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (7.75 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.75 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (7.75 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.75 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Hideshima T, et al. NF-kappa B as a therapeutic target in multiple myeloma. J Biol Chem. 2002 May 10;277(19):16639-47. [2]. Vodanovic-Jankovic S, et al. NF-kappaB as a target for the prevention of graft-versus-host disease: comparative efficacy of bortezomib and PS-1145. Blood. 2006 Jan 15;107(2):827-34. [3]. Oh-I S, et al. Central administration of interleukin-4 exacerbates hypothalamic inflammation and weight gain during high-fat feeding. Am J Physiol Endocrinol Metab. 2010 Jul;299(1):E47-53.

实验参考：

Cell Assay	The inhibitory effect of PS-1145 on MM growth is assessed by measuring MTT dye absorbance of the cells. MM.1S cells are cultured for 48 h with 0.2 and 1 ng/mL TNFα, in the absence or presence of 2.5 μM, 5 μM, and 10 μM PS-1145. Cell viability is assessed by MTT assay. Cells from 48 h cultures are pulsed with 10 μL of 5 mg/mL MTT to each well for the last 4 h of 48-h cultures, followed by 100 μL of isopropanol containing 0.04N HCl. Absorbance is measured at 570 nm using a spectrophotometer[1].
Animal Administration	Mice[2] C57BL/6 (B6), B10.BR, and B6.SJL mice are used. Mice receive regular mouse chow and acidified tap water ad libitum. Bortezomib is administered intravenously to animals at a dose of 1 mg/kg, whereas PS-1145 is given intraperitoneally at a dose of 50 mg/kg. The first dose of each agent is administered before conditioning with total body irradiation (TBI). Rats[3] Weight-matched male Wistar rats (320-350 g) are used. Four groups of rats (n=6/group) consume the HFD for a 9-day study period. Animals in each group receive two consecutive icv injections three times/wk. Immediately prior to icv injection of IL-4 (100 ng) or vehicle, all animals receive a pretreatment icv injection of either the IKKβ inhibitor PS1145 (10 μg) or its vehicle (saline). Food intake and body weight are measured daily. Body composition analysis is conducted as above on days 0 and 8. On day 9, animals are euthanized and samples collected.
References	[1]. Hideshima T, et al. NF-kappa B as a therapeutic target in multiple myeloma. J Biol Chem. 2002 May 10;277(19):16639-47. [2]. Vodanovic-Jankovic S, et al. NF-kappaB as a target for the prevention of graft-versus-host disease: comparative efficacy of bortezomib and PS-1145. Blood. 2006 Jan 15;107(2):827-34.

	[3]. Oh-I S, et al. Central administration of interleukin-4 exacerbates hypothalamic inflammation and weight gain during high-fat feeding. Am J Physiol Endocrinol Metab. 2010 Jul;299(1):E47-53.