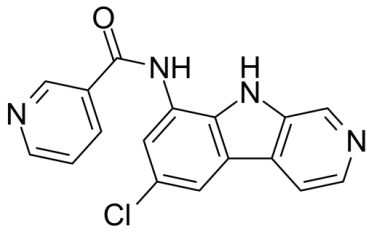
Data Sheet

Product Name:	PS-1145
Cat. No.:	CS-5415
CAS No.:	431898-65-6
Molecular Formula:	C17H11ClN4O
Molecular Weight:	322.75
Target:	Apoptosis; IKK
Pathway:	Apoptosis; NF-κB
Solubility:	DMSO : ≥ 43 mg/mL (133.23 mM); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

PS-1145 is an IκB kinase (**IKK**) inhibitor with an **IC_{50}** of 88 nM. IC50 & Target: IC50: 88 nM (IKK)[1] **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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]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: PS-1145 is resuspended in 10% DMSO and is stored at 4°C for up to 3 days before use[2].[2][3]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.

CAIndexNames:

3-Pyridinecarboxamide, N-(6-chloro-9H-pyrido[3,4-b]indol-8-yl)-

SMILES:

O=C(C1=CC=CN=C1)NC2=CC(Cl)=CC3=C2NC4=C3C=CN=C4

Caution: Product has not been fully validated for medical applications. For research use only.

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