产品名称：PND-1186
产品别名：PND-1186

生物活性：

Description	PND-1186 (VS-4718; SR-2516) is a potent and reversible inhibitor of **FAK** with an **IC_{50}** of 1.5 nM in cell assay.
IC_{50} & Target	IC50: 1.5 nM (FAK)[1]
In Vitro	Using the recombinant FAK kinase domain as a glutathione-S-transferase (GST) fusion protein in an in vitro kinase assay, PND-1186 inhibits FAK activity with IC50 of 1.5 nM. PND-1186 has an IC50 of ~100 nM in breast carcinoma cells as determined by anti-phospho-specific immunoblotting to FAK Tyr-397. Whereas 1.0 μM PND-1186 (>5-fold above IC50) has limited effects on cell proliferation, under non-adherent conditions or when grown as spheroids or colonies in soft agar, 0.1 μM PND-1186 blocks FAK and p130Cas tyrosine phosphorylation, promotes caspase-3 activation, and triggers cell apoptosis. PND-1186 inhibits 4T1 breast carcinoma subcutaneous tumor growth correlated with elevated tumor cell apoptosis and caspase 3 activation[1].
In Vivo	100 mg/kg PND-1186 treatment significantly reduces final 4T1 tumor weight 2-fold (n=8, p<0.05) whereas 30 mg/kg PND-1186 slightly reduces final tumor weight but is not significantly different compare to control (n=8, p>0.05). Both 30 and 100 mg/kg administration of PND-1186 significantly increases tumor TUNEL staining compare to vehicle-treated controls. As elevated cleaved caspase-3 staining is also found in the tumors of PND-1186-treated mice[1]. PND-1186 displays a multi-exponential decay with a terminal half life (t1/2) of 1.72 hours after i.v. injection. Following i.p. and p.o. dosing, PND-1186 is rapidly absorbed with terminal half lives (t1/2) of 2.15 to 2.65 h, and bioavailability (%F) from 14.8 to 42.2%. PND-1186 bioavailability is greater upon intraperitoneal versus oral dosing[2].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 34 mg/mL (67.80 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9940 mL	9.9701 mL	19.9402 mL
	5 mM	0.3988 mL	1.9940 mL	3.9880 mL
	10 mM	0.1994 mL	0.9970 mL	1.9940 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 (4.99 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (4.99 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 (4.99 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.99 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]. Tanjoni I, et al. PND-1186 FAK inhibitor selectively promotes tumor cell apoptosis in three-dimensional environments. Cancer Biol Ther. 2010 May 15;9(10):764-77. [2]. Walsh C, et al. Oral delivery of PND-1186 FAK inhibitor decreases tumor growth and spontaneous breast to lung metastasis in pre-clinical models. Cancer Biol Ther. 2010 May 15;9(10):778-90.

实验参考：

Cell Assay	For cell growth analyses, adherent or suspended cells are treated with PND-1186 for the indicated times, collected as a single cell suspension by limited trypsin treatment, fixed with 70% ethanol, collected by centrifugation and washed with PBS. Cell pellets are resuspended in 300 μL of PBS containing propidium iodide (PI) (10 μg/mL), DNAse-free RNAse (100 μg/mL), and then incubated at 37°C with agitation for 1 h. Samples are analyzed by flow cytometry and cell cycle analyses are performed by ModFit LT3.2 software. Hypodiploid DNA content as a measure of cell apoptosis is detected by PI staining. For cell apoptosis analyses, adherent or suspended cells are treated with PND-1186 and collected as above, stained for phycoerythrin (PE)-conjugated annexin V binding and 7-amino-actinomycin (7-AAD) reactivity, and analyzed within 1 h by flow cytometry. Quadrant gates are positioned based on cell autofluorescence (negative) staurosporine-treated (positive) controls. Apoptosis is calculated to be the percent of annexin V-positive cells. In the soft agar assays, apoptosis is quantified by visual inspection of at least 200 cells and is defined as the appearance of membrane blebbing or cell shrinkage. Apoptosis is also detected by appearance of cleaved caspase-3 antibody reactivity in protein lysates by immunoblotting[1].
Animal Administration	Mice [1] Six to eight week old female C57BL6 and BALB/c mice are used. For subcutaneous tumor growth, 1×10^6 mCherry-labeled 4T1 cells in 100 μL PBS are injected into the hindflank of Balb/C mice. After 8 days, mice with equal volume tumors (as measured using vernier calipers and determined by length×width^2/2) are grouped (n=8 per group) and PND-1186 solubilized in polyethylene glycol 400 (PEG400) in PBS (1:1) is injected (100 μL) subcutaneously in the neck region at 30 mg/kg or 100 mg/kg every 12 hours. Control animals receive PEG400:PBS injections and at 13 days, tumors are imaged in situ using an Olympus OV100 Intravital Fluorescence Molecular Imaging System, tumors are excised and weighed, half is frozen in OCT, and half is solubilized in protein lysis buffer for FAK phosphorylation analyses.
References	[1]. Tanjoni I, et al. PND-1186 FAK inhibitor selectively promotes tumor cell apoptosis in three-dimensional environments. Cancer Biol Ther. 2010 May 15;9(10):764-77. [2]. Walsh C, et al. Oral delivery of PND-1186 FAK inhibitor decreases tumor growth and spontaneous breast to lung metastasis in pre-clinical models. Cancer Biol Ther. 2010 May 15;9(10):778-90.