产品名称：Tiplaxtinin
产品别名：Tiplaxtinin

生物活性：

Description	Tiplaxtinin is a selective and orally efficacious inhibitor of plasminogen activator inhibitor-1 (**PAI-1**) with **IC_{50}** of 2.7 μM.
IC_{50} & Target	IC50: 2.7 μM (PAI-1)[1]
In Vitro	Tiplaxtinin (PAI-039), a small-molecule inhibitor of PAI-1 activity, on the urothelial cell lines. A significant inhibition in cellular proliferation is noted in T24 cells treated with Tiplaxtinin with the documentation of a favorable IC50 value of 43.7±6.3 μM and in UM-UC-14 cells 52.8±1.6 μM whereas the benign cell line, UROtsa, is noted to have a higher IC50 value of 70.3±0.1 μM. Notably, IC50 values of Tiplaxtinin in detached cells, 19.7±3.8 μM in T24, 44.5±6.5 μM in UM-UC-14, and 31.6±6.1 μM in UROtsa, are significantly lower than the IC50 values calculated for cells cultured in the presence of Tiplaxtinin under attached conditions[2].
In Vivo	In the vena cava protocol, Tiplaxtinin (PAI-039) pretreatment significantly reduces thrombus weight at Tiplaxtinin doses of 3, 10 and 30 mg/kg. When Tiplaxtinin is dosed in a treatment paradigm 4 h after stable arterial and venous thrombosis, a significant reduction in thrombus weight is observed 24 h later at Tiplaxtinin doses of 3, 10 and 30 mg/kg[1]. Tiplaxtinin (PAI-039) is administered by oral gavage to athymic mice bearing human bladder cancer cell line T24 xenografts and human cervical cancer HeLa cell xenografts. The subcutaneous tumor growth of both T24 and HeLa cell xenografts treated with Tiplaxtinin is markedly reduced compared with untreated controls. Specifically, at the end of the study, control T24 xenografts are noted to be 1,150±302 mm^3 compared with 593±328 mm^3 for T24 xenograft tumors treated with 5 mg/kg Tiplaxtinin (P<0.0001) and 627±248 mm^3 for T24 xenografts treated with 20 mg/kg (P<0.0001)[2]. Tiplaxtinin (1, 3, and 10 mg/kg) is subjected to electrolytic injury of the coronary artery. Tiplaxtinin (PAI-039) causes prolongation in time to coronary occlusion (control, 31.7±6.3 min; 3 mg/kg Tiplaxtinin, 66.0±6.4 min; 10 mg/kg, 56.7±7.4 min; n=5-6; p<0.05) and a reduced thrombus weight (control, 7.6±1.5 mg; 10 mg/kg Tiplaxtinin, 3.6±1.0 mg; p<0.05)[3].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 54 mg/mL** (**122.90 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	2.2759 mL	11.3797 mL	22.7593 mL
5 mM	0.4552 mL	2.2759 mL	4.5519 mL
10 mM	0.2276 mL	1.1380 mL	2.2759 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 (5.69 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.69 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% (20% SBE-β-CD in saline) Solubility: 2.5 mg/mL (5.69 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (5.69 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 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 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (5.69 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.69 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]. Hennan JK, et al. Effect of Tiplaxtinin (PAI-039), an orally bioavailable PAI-1 antagonist, in a rat model of thrombosis. J Thromb Haemost. 2008 Sep;6(9):1558-64. [2]. Gomes-Giacoia E, et al. Targeting plasminogen activator inhibitor-1 inhibits angiogenesis and tumor growth in a human cancer xenograft model. Mol Cancer Ther. 2013 Dec;12(12):2697-708. [3]. Hennan JK, et al. Evaluation of PAI-039 [{1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1H-indol-3-yl}(oxo)acetic acid], a novel plasminogen activator inhibitor-1 inhibitor, in a canine model of coronary artery thrombosis. J Pharmacol Exp Ther. 2005 Aug;314(2):

实验参考：

Cell Assay	T24, UM-UC-14, UROtsa, and HeLa cells are plated in 96-well dishes in triplicate at 1×10^3 cells per well and allowed to adhere for 24 hours. Subsequently, Tiplaxtinin is added to the wells and allowed to incubate at the indicated concentrations. Cellular proliferation is determined by CellTiter-Glo Luminescent Cell Viability Assay at 24 hours, and IC50 of Tiplaxtinin is determined in Graphpad Prism. Luminescence is measured using a FLUOstar OPTIMA Reader[2].
	Rats[1] Male Sprague-Dawley rats (250-350 g) are dosed orally with either vehicle or Tiplaxtinin (0.3-3 mg/kg) on the morning of the experiment, then anesthetized with sodium-pentobarbital (50 mg/kg, i.p.). A midline incision is made along the neck, and the right and left carotid arteries and jugular veins are exposed. The left jugular vein is catheterized for tPA delivery and blood sampling. The right carotid artery is cannulated with PE-60 tubing filled with 3.8% sodium citrate solution, and interfaced to a saline-filled pressure transducer for monitoring of heart rate and blood pressure. The left carotid artery is used for vascular injury induction and thrombosis. An ultrasonic flow probe is placed on the left carotid artery, and baseline blood flow is recorded. A 3-mm section of PE-60

Animal Administration	tubing is sectioned longitudinally, and a piece of filter paper saturated with 25% $FeCl_3$ is inserted into the tubing. Flow is monitored in the damaged vessel during tPA infusion and for an additional 20 min afterwards. At the end of the experiment, the arterial thrombus is excised and weighed. Mice[2] Mice bearing bladder xenografts and mice bearing cervical xenografts are divided randomly into three groups (control, 5 mg/kg of Tiplaxtinin, and 20 mg/kg of Tiplaxtinin) and treatment is initiated. Each group is composed of at least 10 mice. No toxicity or weight loss is noted in any of the treatment groups. Tiplaxtinin (100 μL diluted in corn oil) is administered via oral gavage daily (Monday-Friday) for 5 weeks. Control mice received vehicle alone on the same schedule. Tumor volumes are measured weekly with digital calipers and calculated. After 5 weeks, the mice are sacrificed, tumors resected, and analyzed by immunohistochemical staining.
References	[1]. Hennan JK, et al. Effect of Tiplaxtinin (PAI-039), an orally bioavailable PAI-1 antagonist, in a rat model of thrombosis. J Thromb Haemost. 2008 Sep;6(9):1558-64. [2]. Gomes-Giacoia E, et al. Targeting plasminogen activator inhibitor-1 inhibits angiogenesis and tumor growth in a human cancer xenograft model. Mol Cancer Ther. 2013 Dec;12(12):2697-708. [3]. Hennan JK, et al. Evaluation of PAI-039 [{1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1H-indol-3-yl}(oxo)acetic acid], a novel plasminogen activator inhibitor-1 inhibitor, in a canine model of coronary artery thrombosis. J Pharmacol Exp Ther. 2005 Aug;314(2):