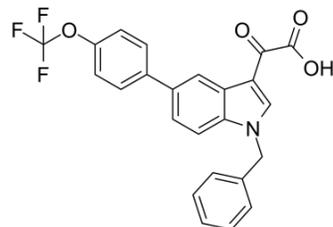


Tiplaxtinin

Cat. No.:	HY-15253		
CAS No.:	393105-53-8		
Molecular Formula:	C ₂₄ H ₁₆ F ₃ NO ₄		
Molecular Weight:	439.38		
Target:	PAI-1; Apoptosis		
Pathway:	Metabolic Enzyme/Protease; Apoptosis		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 54 mg/mL (122.90 mM)
 H₂O : < 0.1 mg/mL (insoluble)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent		1 mg	5 mg	10 mg
	Concentration	Mass			
	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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
Solubility: ≥ 2.5 mg/mL (5.69 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: 2.5 mg/mL (5.69 mM); Suspended solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.5 mg/mL (5.69 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Tiplaxtinin is a selective and orally efficacious inhibitor of plasminogen activator inhibitor-1 (PAI-1) with IC₅₀ of 2.7 μM^[1].

IC₅₀ & 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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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 mm³ compared with 593±328 mm³ for T24 xenograft tumors treated with 5 mg/kg Tiplaxtinin (P<0.0001) and 627±248 mm³ 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].

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PROTOCOL

Cell Assay ^[2]

T24, UM-UC-14, UROtsa, and HeLa cells are plated in 96-well dishes in triplicate at 1×10³ 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].

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Animal Administration ^{[1][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 tubing is sectioned longitudinally, and a piece of filter paper saturated with 25% FeCl₃ 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.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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-Giacoaia 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]. Hennen 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):

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