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产品名称：Arginase inhibitor 1
产品别名：Arginase inhibitor 1

生物活性：

Description	Arginase inhibitor 1 is a potent inhibitor of human arginases I and II with IC_{50}s of 223 and 509 nM, respectively.
IC_{50} & Target	IC50: 223 nM (arginases I), 509 nM (arginases II)[1]
In Vitro	Arginase inhibitor 1inhibits human arginases I and II with IC_{50}s of 223±22.3 and 509±85.1 nM, respectively, and is active in a recombinant cellular assay overexpressing human arginase I (CHO cells). Arginase inhibitor 1 is a novel second generation arginase inhibitor with significant activity in a rat model of myocardial ischemia/reperfusion injury (MI/RI). Arginase inhibitor 1 is potent against hARG I in both in vitro enzyme and cellular assays. The IC_{50} for Arginase inhibitor 1 is 8 μM in CHO Cells Over-Expressing hArgI[1].
In Vivo	A pharmacokinetic evaluation of Arginase inhibitor 1 is conducted after intravenous (i.v.) and oral (p.o.) dosing in male Sprague-Dawley rats (n=3 per dose route). Arginase inhibitor 1 is formulated in 0.9% saline and administered intravenously at 10 mg/kg by bolus through a preimplanted cannula at a dosing volume of 1 mL/kg, and orally at 10 mg/kg via gavage at a dosing volume of 2 mL/kg. Following i.v. dosing with 10 mg/kg in fasted animals, Arginase inhibitor 1has a terminal elimination half-life ($t_{1/2}$) of 3.3 h with a volume of distribution and total body clearance of 1.86 L/kg and 7.89 mL/min/kg, respectively. The oral bioavailability of Arginase inhibitor 1 (10 mg/kg, p.o.) is 28% with a C_{max} of 0.45 mg/L[1].

Solvent&Solubility

In Vitro:

DMSO： ≥ 48 mg/mL (167.73 mM)

H_2O : ≥ 30 mg/mL (104.83 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.4943 mL	17.4715 mL	34.9430 mL
	5 mM	0.6989 mL	3.4943 mL	6.9886 mL
	10 mM	0.3494 mL	1.7472 mL	3.4943 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: ≥ 1.67 mg/mL (5.84 mM); Clear solution

	此方案可获得 ≥ 1.67 mg/mL (5.84 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 16.699999 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: ≥ 1.67 mg/mL (5.84 mM); Clear solution 此方案可获得 ≥ 1.67 mg/mL (5.84 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 16.699999 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: ≥ 1.67 mg/mL (5.84 mM); Clear solution 此方案可获得 ≥ 1.67 mg/mL (5.84 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 16.699999 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Van Zandt MC, et al. Discovery of (R)-2-amino-6-borono-2-(2-(piperidin-1-yl)ethyl)hexanoic acid and congeners as highly potentinhibitors of human arginases I and II for treatment of myocardial reperfusion injury. J Med Chem. 2013 Mar 28;56(6):2568-80.

实验参考：

Animal Administration	Rats[1] Single dose pharmacokinetics are evaluated in male Sprague-Dawley rats by intravenous bolus (i.v.) and oral (p.o.) dosing. Three rats are evaluated per dose group. Arginase inhibitor 1 is freshly formulated in 0.9% saline prior to dosing, at 10 mg/mL for i.v. dosing at a dose volume of 1 mL/kg animal body weight, and at 5 mg/mL for p.o. dosing at a dose volume of 2 mL/kg. Animals are fasted overnight prior to dosing, with water given ad libitum. Arginase inhibitor 1 is administered i.v. through a preimplanted cannula or orally by gavage. Food is reintroduced to animals 4 h following dosing. Blood samples are collected through preimplanted cannulae (dual cannulated animals used for i.v. dosing; blood collection separate from dosing cannula) at 0.25 mL per draw, followed by volume replacement with 0.9% saline. Samples are collected at predose 0.083 (i.v. only), 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h following dosing. Blood samples are maintained on ice and centrifuged at 10 000g to obtain plasma. Plasma is frozen at -20 °C prior to analysis. Analysis is performed by LC/MS/MS using Agilent 1100 HPLC pumps with detection on a PESciex API 4000 Qtrap. Pharmacokinetic evaluation is performed using standard noncompartmental analyses in Phoenix WinNonlin software.
	Purified recombinant full length human arginase I protein and recombinant, fully active, truncated form of human arginase II are used to develop 96-well plate human arginase I and arginase II assays. Inhibition of arginase I and arginase II by program compounds is followed spectrophotometrically at 530 nm. Arginase inhibitor 1 to be tested is dissolved in DMSO at an initial concentration that is 50-fold greater than its final concentration in the cuvette. Ten microliters of the stock solution is diluted in 90 μL of the assay buffer that comprised 0.1 M sodium phosphate buffer

Kinase Assay	containing 130 mM NaCl, pH 7.4, to which is added ovalbumin (OVA) at a concentration of 1 mg/mL. Solutions of arginase I and II are prepared in 100 mM sodium phosphate buffer, pH 7.4, containing 1 mg/mL of OVA to give an arginase stock solution at a final concentration of 100 ng/mL. To each well of a 96-well microtiter plate is added 40 μL of enzyme, 10 μL of the Arginase inhibitor 1 solution, and 10 μL of enzyme substrate solution (L-arginine+Manganese sulfate). For wells that are used as positive controls, only the enzyme and its substrate are added, while wells used as negative controls contained only manganese sulfate. After incubating the microtiter plate at 37°C for 60 min, 150 μL of a urea reagent obtained by combining equal proportions (1:1) of reagents A and B is added to each well of the microtiter plate to stop the reaction. The urea reagent is made just before use by combining Reagent A (10 mM o-phthaldialdehyde and 0.4% polyoxyethylene lauryl ether (w/v) in 1.8 M sulfuric acid) with Reagent B (1.3 mM primaquine diphosphate, 0.4% polyoxyethylene lauryl ether (w/v), and 130 mM boric acid in 3.6 M sulfuric acid). After quenching the reaction mixture, the microtiter plate is allowed to stand for an additional 10 min at room temperature in order to allow color development. The inhibition of arginase is computed by measuring the optical density (OD) of the reaction mixture at 530 nm and normalizing the OD value to percent inhibition observed in the control. The normalized OD is then used to generate a concentation-response curve by plotting the normalized OD values against log[concentration] and using regression analysis to compute the IC50 values[1].
References	[1]. Van Zandt MC, et al. Discovery of (R)-2-amino-6-borono-2-(2-(piperidin-1-yl)ethyl)hexanoic acid and congeners as highly potentinhibitors of human arginases I and II for treatment of myocardial reperfusion injury. J Med Chem. 2013 Mar 28;56(6):2568-80.