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产品名称：Nampt-IN-1
产品别名：LSN3154567

生物活性：

Description	Nampt-IN-1 (LSN3154567) is a potent and selective NAMPT inhibitor. Nampt-IN-1 inhibits purified NAMPT with an IC_{50} of 3.1 nM.
IC_{50} & Target	IC50: 3.1 nM (NAMPT), 0.84 μM (CSF1R)[1]
In Vitro	To assess its selectivity, specificity, and effects on cellular NAD^+ levels, LSN3154567 is characterized in various biochemical and cellular assays. LSN3154567 inhibits purified NAMPT with an IC_{50} of 3.1 nM. When tested against a panel of human kinases (>100; CEREP Kinase panel), it does not exhibit any significant activity (i.e.: IC_{50}≥1 μM) against the kinases tested except CSF1R (IC_{50}≈0.84 μM). LSN3154567 exhibits a broad spectrum of anticancer activity. To assess its anticancer activity, LSN3154567 is tested against a number of different types of cancer cell lines cultured in the absence or presence of nicotinic acid (NA) (10 μM). LSN3154567 exhibits a potent antiproliferative activity against many cell lines in the absence of NA[1].
In Vivo	Nampt-IN-1 (LSN3154567) exhibits good physical chemical properties that allow oral dosing. When dosed orally with 2 mg/kg in mice, it has an exposure of 195 nM*hour in the plasma with a peak concentration of 57 nM (at 0.25 hour) and an oral bioavailability of 39%. When dosed intravenously with 2 mg/kg, it has a hepatic clearance of 158.73 mL/min/kg and a volume of distribution at 7.1 L/kg. The half-life of terminal elimination is estimated to be 2.76 hours. LSN3154567 exhibits a dose-dependent inhibition of NAD^+ formation with estimated TED_{50} value of 2.0 mg/kg. To assess whether LSN3154567 causes retinopathy, rats are treated with LSN3154567 at 20, 40, and 80 mg/kg for 4 days. No apparent retinopathy is observed. The hematological toxicities are observed. When LSN3154567 is dosed at 20, 40, and 80 mg/kg, the plasma exposures obtained are 8,974, 18,061, and 38,327 M*h, respectively. Thus, LSN3154567 exhibits exposure multiples of respective 3-, 7-, and 14-fold over the exposure (2,701 M*h) required for robust efficacy (≈103%) without NA coadministration. Dogs are treated with LSN3154567 at 1 and 2.5 mg/kg. At these dose levels, the retinal toxicity is observed. Degeneration of the outer nuclear layer occurred in all four animals, but is less pronounced in the animals treated with 1 mg/kg. At the 1 and 2.5 mg/kg dose levels, the plasma exposures are determined to be 1,483 and 2,468 nM*h, respectively[1].

In Vitro:

DMSO : ≥ 30 mg/mL (71.52 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3838 mL	11.9192 mL	23.8385 mL
5 mM	0.4768 mL	2.3838 mL	4.7677 mL
10 mM	0.2384 mL	1.1919 mL	2.3838 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。

Solvent&Solubility	***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 (5.96 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.96 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 (5.96 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.96 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 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 (5.96 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.96 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]. Zhao G, et al. Discovery of a Highly Selective NAMPT Inhibitor That Demonstrates Robust Efficacy and Improved Retinal Toxicity with Nicotinic Acid Coadministration. Mol Cancer Ther. 2017 Dec;16(12):2677-2688.

实验参考：

Cell Assay	Cell[1] The cell lines used as following: A2780 and KM-12, KMS-11 and MKN-74, OPM-2 and Kelly; and all other cancer cells. The identity of these cell lines is not tested or verified prior to use in this study. Cells are seeded in 96-well plates, cultured overnight, and treated with LSN3154567 (0.03 to 1,000 nM)±NA (10 μM) in duplicate at 37°C in 5% CO_2 for 72 hours. Staurosporine (10 μM) is used as positive control. Cell viability is determined by a CytoTox-Glo Cytotoxicity assay kit[1].
Animal Administration	Mice[1] Male CD-1 mice are dosed with LSN3154567 at 2 mg/kg intravenously in 20% Captisol (w/v), 25 mmol/L NaPO4, pH 2, q.s. formulation or 2 mg/kg orally in the same vehicle in a cross over design with 3-d wash period in between two arms. Blood samples are obtained through retro orbital at 0, 0.08 (IV only), 0.25, 0.75, 2, 4, 8, and 24 hours and frozen until analysis. For exposure analysis, blood samples (≈20 μL) are obtained through tail clipping at 0.5, 1, 2, 4, 8, and 24 hours. The samples are collected into EDTA-coated capillary tubes and spotted onto Whatman DMPK-C DBS collection cards.

	Rats and Dogs[1] Female rats or male and female dogs are dosed with LSN3154567 orally in the same vehicle. For NA rescue studies, NA is formulated in phosphate buffered saline (pH 7.4). Rats are given LSN3154567 orally once daily at 20, 40, or 80 mg/kg for two cycles of 4 days with 3 days between the first and second cycles. Dogs are also dosed orally at 1 or 2.5 mg/kg (without NA) or at 5 mg/kg (with NA; BID) for 4 days. Exposure is obtained and analyzed as described above.
References	[1]. Zhao G, et al. Discovery of a Highly Selective NAMPT Inhibitor That Demonstrates Robust Efficacy and Improved Retinal Toxicity with Nicotinic Acid Coadministration. Mol Cancer Ther. 2017 Dec;16(12):2677-2688.