产品名称：NMS-1286937
产品别名：NMS-P937

生物活性：

Description

NMS-1286937 is a potent, selective and orally available PLK1 inhibitor, with an IC_{50} of 2 nM.

IC_{50} & Target

PLK1	MELK	CK2	FLT3
2 nM (IC_{50})	744 nM (IC_{50})	826 nM (IC_{50})	510 nM (IC_{50})

In Vitro

NMS-1286937 is a potent, selective and orally available PLK1 inhibitor, with IC_{50} of 2 nM. NMS-1286937 also shows inhibitory activities against FLT3, MELK, and CK2, with IC_{50}s of 510, 744, and 826 nM, respectively[1].. NMS-P937 possesses a pure ATP competitive mechanism with a reversible dissociation and no time dependency. NMS-P937 (10 μM) is selective with a marginal activity of 48% and 40% inhibition on PLK2 and PLK3, respectively. NMS-P937 shows antiproliferative activity against a panel of 137 cell lines, with IC_{50} values of below 100 nM for 60 of 137 cell lines and higher than 1 μM for only 9 of 137 cell lines[2].. NMS-P937 shows cytotoxic activity against AmL-NS8 cells with IC_{50} of 36 nM[3].

Solvent&Solubility

In Vitro:

DMSO : 21 mg/mL (39.44 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8779 mL	9.3893 mL	18.7786 mL
	5 mM	0.3756 mL	1.8779 mL	3.7557 mL
	10 mM	0.1878 mL	0.9389 mL	1.8779 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 mg/mL (3.76 mM); Clear solution

此方案可获得 ≥ 2 mg/mL (3.76 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 20.0 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 mg/mL (3.76 mM); Clear solution

此方案可获得 ≥ 2 mg/mL (3.76 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 20.0 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 mg/mL (3.76 mM); Clear solution 此方案可获得 ≥ 2 mg/mL (3.76 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 20.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Beria I, et al. NMS-P937, a 4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline derivative as potent and selective Polo-like kinase 1 inhibitor. Bioorg Med Chem Lett. 2011 May 15;21(10):2969-74. [2]. Valsasina B, et al. NMS-P937, an orally available, specific small-molecule polo-like kinase 1 inhibitor with antitumor activity in solid and hematologic malignancies. Mol Cancer Ther. 2012 Apr;11(4):1006-16. [3]. Casolaro A, et al. The Polo-Like Kinase 1 (PLK1) inhibitor NMS-P937 is effective in a new model of disseminated primary CD56+ acute monoblastic leukaemia. PLoS One. 2013;8(3):e58424.

实验参考：

Cell Assay	Cells are seeded into 96- or 384-well plates at densities ranging from 10,000 to 30,000/cm^2 for adherent and 100,000/mL for nonadherent cells in appropriate medium supplemented with 10% fetal calf serum. After 24 hours, cells are treated in duplicate with serial dilutions of NMS-P937, and 72 hours later, the viable cell number is assessed by the CellTiter-Glo Assay. IC_{50} values are calculated with a sigmoidal fitting algorithm. Experiments are carried out independently at least twice. [2]
Animal Administration	For carcinoma xenograft studies, 5- to 6-week-old female Hsd, athymic nu/nu mice (average weight, 20-22 g), are used. HCT116, HT29, Colo205 colorectal, and A2780 ovarian human carcinoma cell lines are inoculated subcutaneously. Mice bearing a palpable tumor (100-200 mm^3) are treated with vehicle or NMS-P937 following doses and schedules starting from the day after randomization. Tumor dimensions are measured regularly with Vernier calipers, and tumor growth inhibition (TGI) is calculated. Toxicity is evaluated on the basis of body weight reduction. For leukemia studies, 5- to 6-week-old female severe combined immunodeficient mice (SCID; average weight, 20-22 g) are used. The AmL cell line HL-60 (5×10^6 cells) is injected subcutaneously and treatments initiated when tumor size reaches 200 to 250 mm^3. Tumor dimensions and TGI are assessed. For disseminated models, 5×10^6 AmL primary cells (AmL-PS) are injected intravenously and treatments start after 2 days. Mice are monitored daily for clinical signs of disease, and the median survival time is determined for each group. [2]
Kinase Assay	The inhibitory activity of putative kinase inhibitors and the potency of selected compounds are determined using a trans-phosphorylation assay. Specific peptide or protein substrates are trans-phosphorylated by their specific serine-threonine or tyrosine kinase, in the presence of ATP traced with ^{33}P-γ-ATP, at optimized buffer and cofactors conditions. At the end of the phosphorylation reaction, more than 98% unlabeled ATP and radioactive ATP is captured by adding an excess of the ion exchange dowex resin; the resin then settles down to the bottom of the reaction plate by gravity. Supernatant, containing the phosphorylated substrate, is subsequently withdrawn and transferred into a counting plate, followed by evaluation by b-counting. Inhibitory potency evaluation for all the tested kinases is performed at 25°C using a 60 min end-point assay where the concentrations of ATP and substrates are kept equal to 2 × αK_m and saturated (>5 × αK_m), respectively. [1]
	[1]. Beria I, et al. NMS-P937, a 4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline derivative as potent and selective Polo-like kinase 1 inhibitor. Bioorg Med Chem Lett. 2011 May 15;21(10):2969-74.

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