产品名称： N-[4-[[3-(2-氨基-4-嘧啶基)-2-吡啶基]氧基]苯基]-4-(4-甲基-2-噻吩基)-1-酞嗪胺

产品别名： AMG 900

生物活性：

Description	AMG 900 is a potent and highly selective pan-Aurora kinases inhibitor with IC_{50} of 5 nM, 4 nM and 1 nM for Aurora A, B and C, respectively.		
IC_{50} & Target	Aurora A	Aurora B	Aurora C
	5 nM (IC_{50})	4 nM (IC_{50})	1 nM (IC_{50})
In Vitro	AMG 900 inhibits the enzyme activity of all 3 aurora kinase family members with IC_{50} values of 5 nM or less. In HeLa cells, AMG 900 inhibits autophosphorylation of aurora-A and -B in a concentration-dependent manner. Treatment of HCT116 cells with 50 nM of AMG 900 for 48 hours resulted in polyploidy and suppresses the formation of colonies after cell replating. AMG 900 inhibits cell proliferation, with EC_{50} values ranging from 0.7 to 5.3 nM. Importantly, 4 of these AMG 900-sensitive cell lines (HCT-15, MES-SA-Dx5, 769P, and SNU449) are resistant to paclitaxel and other anticancer agents. AMG 900 inhibits p-histone H3 or induced polyploidy across all the cell lines tested irrespective of P-gp or BCRP status with uniform potency (IC_{50} or EC_{50} values ranging from 2 to 3 nM) [1].		
In Vivo	AMG 900 exhibits significant antitumor activity in all 9 xenograft models tested (50%-97% TGI compared with the vehicle-treated control group, P<0.005, P<0.0005). Importantly, AMG 900 is active in the MES-SA-Dx5 (84% TGI, P<0.0001) and NCI-H460-PTX (66% TGI, P<0.0001) xenograft models that are resistant to either Docetaxel or Paclitaxel administered at their respective maximum tolerated doses. AMG 900 inhibits the activity of aurora-B in HCT116 tumors and suppresses the growth of multiple xenografts that represent diverse tumor types[1]. Treatment with AMG 900 at 15 mg/kg significantly inhibits p-Histone H3 in the G_2M cell population in mouse bone marrow (upper panel) and cytokeratin positive COLO 205 tumor (lower panel) compared with vehicle-treated controls[2]. AMG 900 exhibits a low-to-moderate clearance and a small volume of distribution. Its terminal elimination half-life ranged from 0.6 to 2.4 h. AMG 900 is well-absorbed in fasted animals with an oral bioavailability of 31% to 107%. Food intake had an effect on rate (rats) or extent (dogs) of AMG 900 oral absorption[3].		
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 50 mg/mL (99.29 mM)** * "≥" means soluble, but saturation unknown.		

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9858 mL	9.9289 mL	19.8578 mL
	5 mM	0.3972 mL	1.9858 mL	3.9716 mL
	10 mM	0.1986 mL	0.9929 mL	1.9858 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: ≥ 5 mg/mL (9.93 mM); Clear solution 此方案可获得 ≥ 5 mg/mL (9.93 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 50.0 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: ≥ 5 mg/mL (9.93 mM); Clear solution 此方案可获得 ≥ 5 mg/mL (9.93 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 50.0 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。
References	[1]. Payton M, et al. Preclinical evaluation of AMG 900, a novel potent and highly selective pan-aurora kinase inhibitor with activity in taxane-resistant tumor cell lines. Cancer Res, 2010, 70(23), 9846-9854. [2]. Juan G, et al. AMG 900, a potent inhibitor of aurora kinases causes pharmacodynamic changes in p-Histone H3 immunoreactivity in human tumor xenografts and proliferating mouse tissues. J Transl Med. 2014 Nov 4;12:307. [3]. Huang L, et al. In vitro and in vivo pharmacokinetic characterizations of AMG 900, an orally bioavailable small molecule inhibitor of aurora kinases. Xenobiotica. 2011 May;41(5):400-8.

实验参考：

Cell Assay	Different tumor cell lines including NCI-H460, MDA-MB231, MES-SA, NCI-H460 PTX, MDA-MB-231 PTX, MES-SA Dx5, and HCT-15. are treated with AMG 900 (0.5, 5.0, 50 nM) for 48 hours, washed twice with complete media, and cells are replated at a density of 5000 cells per well in drug-free complete media. Cells are grown until the DMSO control wells are confluent. Cells are stained with crystal violet dye, washed with distilled water, and imaged using a digital scanner[1].
Animal Administration	Mice[2]. Female athymic nude mice of approximately 14 weeks of age are used. Mice are injected subcutaneously with 2×10^6 COLO 205 cells in 100 μL of 50% matrigel. Mice with established tumors (approximately 200 mm^3) are assigned into experimental groups (n=10 per group) and administered a single oral dose of vehicle or AMG 900 at 3.75, 7.5, and 15 mg/kg. Three hours after treatment tissue specimens (bone marrow, tumor, and skin) are collected from individual mice for pharmacodynamic and histological analysis. Blood plasma samples (50 μL) are collected from individual mice to determine the concentration of AMG 900 using quantitative methods. Excised tumors are divided in half for parallel flow and imaging based cytometric analyses. Rats[3]. Effect of food intake on AMG 900 PK is evaluated in male rats and male dogs following a single oral dose of AMG 900 at 5 mg/kg (rats) or 2 mg/kg (dogs) in the oral formulation mentioned above. For the rats, food is removed ~16 h before dosing for the fasted group, although the fed group had free access to standard laboratory rodent chow throughout the study; food is returned to rats in the fasted group 2 h post-dose. All the dogs are fasted for ~16 h before dosing. Each dog in the fed group receive 350 g of moist food 1 h prior to dosing, and any remaining food is removed after 1 h.

	All the dogs are fed 2 h post-dose.
References	[1]. Payton M, et al. Preclinical evaluation of AMG 900, a novel potent and highly selective pan-aurora kinase inhibitor with activity in taxane-resistant tumor cell lines. Cancer Res, 2010, 70(23), 9846-9854. [2]. Juan G, et al. AMG 900, a potent inhibitor of aurora kinases causes pharmacodynamic changes in p-Histone H3 immunoreactivity in human tumor xenografts and proliferating mouse tissues. J Transl Med. 2014 Nov 4;12:307. [3]. Huang L, et al. In vitro and in vivo pharmacokinetic characterizations of AMG 900, an orally bioavailable small molecule inhibitor of aurora kinases. Xenobiotica. 2011 May;41(5):400-8.