产品名称：6-[4-[(4-乙基-1-哌嗪)甲基]苯基]-N-[(1R)-1-苯基乙基]-7H-吡咯并[2,3-D]嘧啶-4-胺
产品别名：AEE788

生物活性：

Description	AEE788 is an inhibitor of the EGFR and ErbB2 with IC_{50} values of 2 and 6 nM, respectively.	
IC_{50} & Target	EGFR	ErbB2
	2 nM (IC_{50})	6 nM (IC_{50})
In Vitro	AEE788 inhibits EGFR and VEGF receptor tyrosine kinases in the nM range (IC50:EGFR 2 nm, ErbB2 6 nm, KDR 77 nm, and Flt-1 59 nm). In cells, growth factor-induced EGFR and ErbB2 phosphorylation is also efficiently inhibited (IC50:11 and 220 nm, respectively). AEE788 demonstrates antiproliferative activity against a range of EGFR and ErbB2-overexpressing cell lines (including EGFRvIII-dependent lines) and inhibits the proliferation of epidermal growth factor- and VEGF-stimulated human umbilical vein endothelial cells[1]. Treatment of cutaneous SCC cells with AEE788 leads to dose-dependent inhibition of EGFR and VEGFR-2 phosphorylation, growth inhibition, and induction of apoptosis[2].	
In Vivo	AEE788 efficiently inhibits growth factor-induced EGFR and ErbB2 phosphorylation in tumors for >72 h. AEE788 also inhibits VEGF-induced angiogenesis in a murine implant model[1]. In mice treated with AEE788, tumor growth is inhibited by 54% at 21 days after the start of treatment compared with control mice[2].	

Solvent&Solubility

In Vitro:

DMSO : 50 mg/mL (**113.49 mM;** Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2697 mL	11.3487 mL	22.6974 mL
	5 mM	0.4539 mL	2.2697 mL	4.5395 mL
	10 mM	0.2270 mL	1.1349 mL	2.2697 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: ≥ 2.5 mg/mL (5.67 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.67 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 (5.67 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (5.67 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 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 (5.67 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.67 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]. Traxler P, et al. AEE788: a dual family epidermal growth factor receptor/ErbB2 and vascular endothelial growth factor receptor tyrosine kinase inhibitor with antitumor and antiangiogenic activity. Cancer Res. 2004 Jul 15;64(14):4931-4941. [2]. Park et al. AEE788, a dual tyrosine kinase receptor inhibitor, induces endothelial cell apoptosis in human cutaneous squamous cell carcinoma xenografts in nude mice. Clin Cancer Res. 2005 Mar 1;11(5):1963-1973.

实验参考：

Cell Assay	AEE788 is dissolved in 90% polyethylene glycol 300 plus 10% 1-methyl-2-pyrrolidinone to a concentration of 6.25 mg/mL. Tumor cells are seeded into 96-well plates in complete medium and allowed to attach for 24 hours. The cultures are re-fed with medium with 2% serum. After 24 hours, cells are treated with different concentrations (0-2 μM) of AEE788 (negative control with DMSO alone) for 72 hours. After a 2-hour incubation in medium containing 0.42 mg/mL MTT, the cells are lysed in 100 μL DMSO. The conversion of MTT to formazan is measured at an absorbance of 570 nm[2]
Animal Administration	Mice: AEE788 is diluted in DMSO and diluted in the optimal medium. BALB/c mice bearing s.c. A-431 squamous tumors (3 animals/group) or HC11-NeuT-driven breast tumors (2 animals/group) are dosed orally with 30 mg/kg of AEE788 or vehicle once daily for 5 days. At different time points after the end of compound treatment and before sacrificing the animals the mice are given i.v. 500 μg EGF/kg body weight or 0.2 ml 0.9% w/v NaCl as vehicle control. Five min after EGF administration, the mice are sacrificed, tumors are removed[1].
Kinase Assay	The *invitro* kinase assays are performed in 96-well plates (30 μL) at ambient temperature for 15–45 min using the recombinant glutathione S-transferase-fused kinase domains (4–100 ng, depending on specific activity). [γ^{33}P]ATP is used as phosphate donor and polyGluTyr-(4:1) peptide as acceptor. Assays are optimized for each kinase using the following ATP concentrations: 1.0 μM (c-Kit, c-Met, c-Fms, c-Raf-1, and RET), 2.0 μM (EGFR, ErbB2, ErbB3, and ErbB4), 5.0 μM (c-Abl), 8.0 μM (Flt-1, Flt-3, Flt-4, Flk, KDR, FGFR-1, and Tek), 10.0 μM (PDGF receptor-β, protein kinase C-α, and cyclin-dependent kinase 1), and 20.0 μM (c-Src and protein kinase A). The reaction is terminated by the addition of 20 μL 125 mM EDTA. Thirty μL (c-Abl, c-Src, insulin-like growth factor-1R, RET-Men2A, and RET-Men2B) or 40 μL (all other kinases) of the reaction mixture is transferred onto Immobilon-polyvinylidene difluoride membrane, presoaked with 0.5% H3PO4 and mounted on a vacuum manifold. Vacuum is then applied and each well rinsed with 200 μL 0.5% H_3PO_4. Membranes are removed and washed four times. Dried membranes are counted. IC_{50} are

	calculated by linear regression analysis of the percentage inhibition and are averages of at least three determinations [1].
References	[1]. Traxler P, et al. AEE788: a dual family epidermal growth factor receptor/ErbB2 and vascular endothelial growth factor receptor tyrosine kinase inhibitor with antitumor and antiangiogenic activity. Cancer Res. 2004 Jul 15;64(14):4931-4941. [2]. Park et al. AEE788, a dual tyrosine kinase receptor inhibitor, induces endothelial cell apoptosis in human cutaneous squamous cell carcinoma xenografts in nude mice. Clin Cancer Res. 2005 Mar 1;11(5):1963-1973.