产品名称：**E-3810**
产品别名：**Lucitanib；德立替尼**

生物活性：

Description	Lucitanib (E-3810) is a novel dual inhibitor of VEGFR and FGFR, potently and selectively inhibits VEGFR1, VEGFR2, VEGFR3, FGFR1 and FGFR2 with IC_{50}s of 7 nM, 25 nM, 10 nM, 17.5 nM, and 82.5 nM, respectively.

IC_{50} & Target

VEGFR1	VEGFR2	VEGFR3	FGFR1	FGFR2
7 nM (IC_{50})	25 nM (IC_{50})	10 nM (IC_{50})	17.5 nM (IC_{50})	82.5 nM (IC_{50})

In Vitro

Consistent with the inhibitory activity of VEGFR and FGFR auto-phosphorylation, Lucitanib potently inhibits VEGF and bFGF-stimulated HUVEC proliferation with IC50 of 40 and 50 nM, respectively. Besides, Lucitanib (E-3810) also inhibits CSF-1R with IC50 of 5 nM[1]. Lucitanib potently inhibits FGFR2 activity (Ki<0.05 μM), follows by PDGFRα activity (Ki=0.11 μM). The Ki values obtained for DDR2, LYN, CARDIAK, CSBP (2), EPHA2, and YES range between 0.26 and 8 μM[2].

In Vivo

Lucitanib (E-3810), at oral dosing of 20 mg/kg for 7 consecutive days, completely inhibits (P<0.01) the bFGF induced angiogenic response compare with the response in vehicle-treated mice. Lucitanib (E-3810) shows a broad spectrum of activity, being active in all the xenografts tested (HT29 colon carcinoma, A2780 ovarian carcinoma, A498, SN12K1, and RXF393 renal carcinomas) with dose-dependent inhibition of tumor growth. E-3810 significantly delays growth during treatment, but tumors resume their growth when treatment is suspended; in a few cases, tumor regression is observed[1]. The activity of Lucitanib (E-3810) given at the doses of 15 mg/kg is tested on MDA-MB-231 breast cancer transplanted subcutaneously, at a late stage, when tumor masses reach 350 to 400 mg. This tumor xenograft is very sensitive to Lucitanib (E-3810), with complete tumor stabilization lasting throughout the 30-day treatment. As in other tumor models, tumors re-grow after withdrawal of Lucitanib (E-3810) at a rate similar to control tumors[3].

Solvent&Solubility

In Vitro:

DMSO： ≥ 25 mg/mL (56.37 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2548 mL	11.2742 mL	22.5484 mL
	5 mM	0.4510 mL	2.2548 mL	4.5097 mL
	10 mM	0.2255 mL	1.1274 mL	2.2548 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 (5.64 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.64 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 (5.64 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.64 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 (5.64 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.64 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]. Bello E, et al. E-3810 is a potent dual inhibitor of VEGFR and FGFR that exerts antitumor activity in multiple preclinical models. Cancer Res. 2011 Feb 15;71(4):1396-405. [2]. Colzani M, et al. Quantitative chemical proteomics identifies novel targets of the anti-cancer multi-kinase inhibitor E-3810. Mol Cell Proteomics. 2014 Jun;13(6):1495-509. [3]. Bello E, et al. The tyrosine kinase inhibitor E-3810 combined with paclitaxel inhibits the growth of advanced-stage triple-negative breast cancer xenografts. Mol Cancer Ther. 2013 Feb;12(2):131-40

实验参考：

Cell Assay	Exponentially growing HUVEC or NHI3T3 cells are seeded into 96-well plates at a density of 3 to 6×10^3 cells/100 μL/well in complete medium. In the experiments without serum starvation, 24 hours after seeding, cells are exposed to different Lucitanib (E-3810) concentrations without or with $VEGF_{165}$ (50 ng/mL) or bFGF (20 ng/mL) ligands and the antiproliferative effect of the drugs is evaluated after 72 hours by MTS Colorimetric Assay. In the assays with serum starvation conditions, 24 hours after seeding complete medium is removed and after 3 rounds of washing with PBS, cells are cultured in medium containing 1% BSA. After 18 to 24 hours, cells are processed. Exponentially growing A2780, A498, SN12KI, and HepG2 cells are seeded into 96-well plates at 3 to 5×10^3 cells/100 μL/well in complete medium. Twenty-four hours later cells are treated with different drug concentrations for 72 hours and the antiproliferative effect is evaluated by MTS[1]
Animal Administration	Mice[3] MDA-MB-231 tumor-bearing mice are randomized when their tumor masses are about 350 to 400 mg to receive Lucitanib (E-3810) (15 mg/kg), Brivanib, and Sunitinib at the doses used for the antitumor activity trial, for 10 days. Four hours after the antiangiogenic dose of day 7, Paclitaxel is injected intravenously at the dose of 20 mg/kg and tumor and plasma samples are collected after 1, 4, and 24 hours in all the groups (each group consisting of 3 animals). At the indicated sampling time, mice are anesthetized, blood is collected from the retro-orbital plexus into heparinized tubes, and the plasma fraction is separated. Mice are killed by cervical dislocation, and tumors excised and snap-frozen. The samples are analyzed by high-performance liquid chromatography (HPLC) with UV detection at 230 nm.

References	[1]. Bello E, et al. E-3810 is a potent dual inhibitor of VEGFR and FGFR that exerts antitumor activity in multiple preclinical models. Cancer Res. 2011 Feb 15;71(4):1396-405. [2]. Colzani M, et al. Quantitative chemical proteomics identifies novel targets of the anti-cancer multi-kinase inhibitor E-3810. Mol Cell Proteomics. 2014 Jun;13(6):1495-509. [3]. Bello E, et al. The tyrosine kinase inhibitor E-3810 combined with paclitaxel inhibits the growth of advanced-stage triple-negative breast cancer xenografts. Mol Cancer Ther. 2013 Feb;12(2):131-40