产品名称：**Tipifarnib**
产品别名：替吡法尼

生物活性：	
Description	Tipifarnib (R115777; IND 58359) is a nonpeptidomimetic quinolinone with potential antineoplastic activity. Tipifarnib (R115777; IND 58359) binds to and inhibits farnesyltransferase (FTase) with IC50 of 0.6 nM.
IC_{50} & Target	IC50: 0.6 nM (FTase)
In Vitro	Tipifarnib (5 μM) leads the percentage of apoptotic cells significantly higher in drug-treated compared to DMSO-treated LGL T-cells. Using T-cells from healthy donors, tipifarnib reduces the percentage of IFNγ-positive cells in a time-dependent manner. Tipifarnib reduces the amount of activated Ras in precipitates compared to DMSO[2]. Tipifarnib exerts selective in vitro toxicity against clonal MDS hematopoiesis at concentrations less than 10 nM the effect being more prominent in white cell progenitors. This action is not due to apoptosis induction as both normal and MDS progenitors displays equivalent DiOC3 and annexin V expression up to 72 hours after exposure to Tipifarnib[3]. Combining Tipifarnib with 10 nM 4-OH-tamoxifen in the presence of E2 reduces the IC50 8-fold from 400 to 50 nM[4]. Tipifarnib induces apoptosis in U937 cells[5]. In addition, Tipifarnib inhibits isolated human farnesyltransferase for a lamin B peptide and for the K-RasB peptide with IC50 of 0.86 nM and 7.9 nM, respectively[6].
In Vivo	Tipifarnib has the light of the modest toxicity in patients and the potent reduction of graft-versus-host disease in mice, and it could help to reduce graft-versus-host disease significantly without having a negative impact on immune reconstitution[1]. Combined therapy with tamoxifen and Tipifarnib (50 mg/kg, p.o.) produces greater tumor growth inhibition when compared with either drug alone. E2 deprivation and Tipifarnib in combination results in greater growth inhibition than either E2 deprivation or Tipifarnib alone. The combination of tamoxifen and Tipifarnib results in significantly lower Ki-67 compared with either tamoxifen or Tipifarnib alone. Tipifarnib alone also reduces the CTI compared with control. The combination of tamoxifen and Tipifarnib or Tipifarnib coupled with E2 withdrawal is most effective at lowering the CTI (0.8 and 0.7, respectively), which may account for the decrease in tumor volume[4].
Solvent&Solubility	***In Vitro:*** **DMSO : 33.33 mg/mL (68.10 mM; Need ultrasonic)**

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0433 mL	10.2166 mL	20.4332 mL
5 mM	0.4087 mL	2.0433 mL	4.0866 mL
10 mM	0.2043 mL	1.0217 mL	2.0433 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: ≥ 2.75 mg/mL (5.62 mM); Clear solution 此方案可获得 ≥ 2.75 mg/mL (5.62 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 27.5 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: ≥ 2.75 mg/mL (5.62 mM); Clear solution 此方案可获得 ≥ 2.75 mg/mL (5.62 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 27.5 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: ≥ 2.75 mg/mL (5.62 mM); Clear solution 此方案可获得 ≥ 2.75 mg/mL (5.62 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 27.5 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Hechinger AK, et al. Inhibition of protein geranylgeranylation and farnesylation protects against GvHD via effects on CD4 effector T cells. Haematologica. 2012 Jul 16. [2]. Bai F, et al. Tipifarnib-mediated suppression of T-bet-dependent signaling pathways. Cancer Immunol Immunother. 2012 Apr;61(4):523-33. [3]. Kotsianidis I, et al. In vitro effects of the farnesyltransferase inhibitor tipifarnib on myelodysplastic syndrome progenitors. Acta Haematol. 2008;120(1):51-6 [4]. Martin LA, et al. The farnesyltransferase inhibitor R115777 (tipifarnib) in combination with tamoxifen acts synergistically to inhibit MCF-7 breast cancer cell proliferation and cell cycle progression in vitro and in vivo. Mol Cancer Ther. 2007 Sep;6(9):2 [5]. Krzykowska-Petitjean K, et al. Tipifarnib and tanespimycin show synergic proapoptotic activity in U937 cells. J Cancer Res Clin Oncol. 2012 Mar;138(3):537-44. [6]. End DW, et al. Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. Cancer Res. 2001 Jan 1;61(1):131-7

实验参考：

Cell Assay	Steroid-depleted cells are seeded into 12-well plates at a density of appr 1×10^4 cells per well or into 96-well plates at a density of 4,000 cells per well, in dextran-coated charcoal medium. After 24 h, monolayers are treated with E2 plus inhibitors either alone or in combination. The 12-well plates are treated for 6 days with daily changes. Cell number is then determined using a Z1 Coulter counter. The 96-well plates are treated with a single dose and left for 96 h at which time cell viability is measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay as described previously. The interaction between Tipifarnib and 4-OH-tamoxifen is analyzed by the median effect plot method described by Chou and Talalay. Calculation of the combination index took into account a nonfixed drug ratio and is based on the assumption that the action of the two drugs is mutually nonexclusive for the strict detection of synergism. A combination index < 1 indicates synergism, combination index=1 indicates additivity, and a combination index > 1 indicates antagonism.

	Experiments are repeated thrice. [4]
Animal Administration	Female ovariectomized Ncr foxhead nude mice are kept under sterile conditions with free access to food and water. MCF-7 xenografts are initiated by implantation of 2-mm diameter tumor fragments from established tumors. Tumor growth is maintained by E2 supplementation through i.d. injection of 17β-estradiol pellets (dose 1.7 mg over 60 days). Once tumors reach a diameter of appr 7 mm, mice are randomized to receive vehicle [20% w/v β-cyclodextrin (pH 2.5) for Tipifarnib, 50% PEG 300, 50% H_2O + 1 drop 1N HCl per 3 mL for tamoxifen], Tipifarnib (50 mg/kg twice daily), tamoxifen (20 mg/kg), or a combination of both Tipifarnib and tamoxifen. Two further treatment arms are used to assess the effect of E2 withdrawal (removal of the E2 pellet) or E2 withdrawal combined with Tipifarnib (50 mg/kg twice daily). All drugs are given by oral gavage daily for 5 consecutive days followed by a 2-day rest period, for a total of 19 days. The experiment is done twice giving similar results; therefore, the growth data are combined for statistical analysis. There are six tumor-bearing animals in each group and all tumors are harvested on day 19. Tumor volumes are calculated using the formula $a \times b^2 \times \pi/6$, where a and b are orthogonal tumor diameters and expressed as a percentage of the volume at the start of treatment (relative tumor volume). Overall statistical difference is calculated using the Kruskal-Wallace test and statistical differences between individual treatment arms are calculated using the Mann-Whitney test. [4]
References	[1]. Hechinger AK, et al. Inhibition of protein geranylgeranylation and farnesylation protects against GvHD via effects on CD4 effector T cells. Haematologica. 2012 Jul 16. [2]. Bai F, et al. Tipifarnib-mediated suppression of T-bet-dependent signaling pathways. Cancer Immunol Immunother. 2012 Apr;61(4):523-33. [3]. Kotsianidis I, et al. In vitro effects of the farnesyltransferase inhibitor tipifarnib on myelodysplastic syndrome progenitors. Acta Haematol. 2008;120(1):51-6 [4]. Martin LA, et al. The farnesyltransferase inhibitor R115777 (tipifarnib) in combination with tamoxifen acts synergistically to inhibit MCF-7 breast cancer cell proliferation and cell cycle progression in vitro and in vivo. Mol Cancer Ther. 2007 Sep;6(9):2 [5]. Krzykowska-Petitjean K, et al. Tipifarnib and tanespimycin show synergic proapoptotic activity in U937 cells. J Cancer Res Clin Oncol. 2012 Mar;138(3):537-44. [6]. End DW, et al. Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. Cancer Res. 2001 Jan 1;61(1):131-7