

产品名称：**N-Desethyl Sunitinib**

产品别名：**N-去乙基-舒尼替尼**

生物活性:					
Description	N-Desethyl Sunitinib is a metabolite of sunitinib. Sunitinib is a potent, ATP-competitive VEGFR, PDGFRβ and KIT inhibitor with Ki values of 2, 9, 17, 8 and 4 nM for VEGFR -1, -2, -3, PDGFRβ and KIT, respectively.				
In Vitro	Sunitinib also potently inhibits Kit and FLT-3[1]. Sunitinib is a potent ATP-competitive inhibitor of VEGFR2 (Flk1) and PDGFRβ with Ki of 9 nM and 8 nM, respectively, displaying >10-fold higher selectivity for VEGFR2 and PDGFR than FGFR-1, EGFR, Cdk2, Met, IGFR-1, Abl, and src. In serum-starved NIH-3T3 cells expressing VEGFR2 or PDGFRβ, Sunitinib inhibits VEGF-dependent VEGFR2 phosphorylation and PDGF-dependent PDGFRβ phosphorylation with IC50 of 10 nM and 10 nM, respectively. Sunitinib inhibits VEGF-induced proliferation of serum-starved HUVECs with IC50 of 40 nM, and inhibits PDGF-induced proliferation of NIH-3T3 cells overexpressing PDGFRβ or PDGFRα with IC50 of 39 nM and 69 nM, respectively[2]. Sunitinib inhibits phosphorylation of wild-type FLT3, FLT3-ITD, and FLT3-Asp835 with IC50 of 250 nM, 50 nM, and 30 nM, respectively. Sunitinib inhibits the proliferation of MV4;11 and OC1-AML5 cells with IC50 of 8 nM and 14 nM, respectively, and induces apoptosis in a dose-dependent manner[3].				
In Vivo	Sunitinib (20-80 mg/kg/day) exhibits broad and potent dose-dependent anti-tumor activity against a variety of tumor xenograft models including HT-29, A431, Colo205, H-460, SF763T, C6, A375, or MDA-MB-435, consistent with the substantial and selective inhibition of VEGFR2 or PDGFR phosphorylation and signaling in vivo. Sunitinib (80 mg/kg/day) for 21 days leads to complete tumor regression in six of eight mice, without tumor re-growing during a 110-day observation period after the end of treatment. Second round of treatment with Sunitinib remains efficacious against tumors that are not fully regressed during the first round of treatment. Sunitinib treatment results in significant decrease in tumor MVD, with appr 40% reduction in SF763T glioma tumors. SU11248 treatment results in a complete inhibition of additional tumor growth of luciferase-expressing PC-3M xenografts, despite no reduction in tumor size[2]. Sunitinib treatment (20 mg/kg/day) dramatically suppresses the growth subcutaneous MV4;11 (FLT3-ITD) xenografts and prolongs survival in the FLT3-ITD bone marrow engraftment model[3].				
Solvent&Solubility	In Vitro: DMSO : 50 mg/mL (134.98 mM; Need ultrasonic)				
	Solvent Mass Concentration	1 mg	5 mg	10 mg	
	Preparing	1 mM	2.6996 mL	13.4982 mL	26.9964 mL
	Stock Solutions	5 mM	0.5399 mL	2.6996 mL	5.3993 mL
		10 mM	0.2700 mL	1.3498 mL	2.6996 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℃, 6 months; -20℃, 1 month。 -80℃ 储存时，请在 6 个月内使用， -20℃ 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 (6.75 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.75 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 (6.75 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.75 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 (6.75 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.75 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]. Sun L, et al. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor r [2]. Mendel DB, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Can [3]. O'Farrell AM, et al. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood. 2003 May 1;101(9):3597-605. Epub 2003 Jan 16.
实验参考：	
Cell Assay	Cells are starved overnight in medium containing 0.1% FBS prior to addition of Sunitinib and FL (50 ng/mL; FLT3-WT cells only). Proliferation is measured after 48 hours of culture using the Alamar Blue assay or trypan blue cell viability assays. Apoptosis is measured 24 hours after Sunitinib addition by Western blotting to detect cleavage of poly (ADP-ribose) polymerase (PARP) or levels of caspase-3. [3]
	IC₅₀ values for Sunitinib against VEGFR2 (Flk-1) and PDGFRβ are determined using glutathione S-transferase fusion proteins containing the complete cytoplasmic domain of the RTK. Biochemical tyrosine kinase assays to quantitate the trans-phosphorylation activity of VEGFR2 (Flk-1) and PDGFRβ are performed in 96-well microtiter plates precoated (20 μg/well in PBS; incubated overnight at 4°C) with the peptide substrate poly-Glu,Tyr (4:1). Excess protein binding sites are blocked with the addition of 1-5% (w/v) BSA in PBS. Purified GST-fusion proteins are produced in baculovirus-infected insect cells. GST-VEGFR2 and GST-PDGFRβ are then added to the microtiter wells in 2$\times$ concentration kinase dilution buffer consisting of 100 mM HEPES, 50 mM NaCl, 40 mM NaVO₄, and 0.02% (w/v) BSA. The final enzyme concentration for GST-VEGFR2 or GST-PDGFRβ is 50 ng/mL. Twenty-five μL of diluted sunitinib are subsequently added to each reaction well to produce a range of inhibitor concentrations appropriate for each enzyme. The kinase reaction is

Kinase Assay	initiated by the addition of different concentrations of ATP in a solution of $MnCl_2$ so that the final ATP concentrations spanned the K_m for the enzyme, and the final concentration of $MnCl_2$ is 10 mM. The plates are incubated for 5-15 minutes at room temperature before stopping the reaction with the addition of EDTA. The plates are then washed three times with TBST. Rabbit polyclonal antiphosphotyrosine antisera are added to the wells at a 1:10,000 dilution in TBST containing 0.5% (w/v) BSA, 0.025% (w/v) nonfat dry milk, and 100 μM $NaVO_4$ and incubated for 1 hour at 37°C. The plates are then washed three times with TBST, followed by the addition of goat antirabbit antisera conjugated with horseradish peroxidase (1:10,000 dilution in TBST). The plates are incubated for 1 hour at 37°C and then washed three times with TBST. The amount of phosphotyrosine in each well is quantitated after the addition of 2,2'-azino-di-[3-ethylbenzthiazoline sulfonate] as substrate. [1]
References	[1]. Sun L, et al. <u>Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor r</u> [2]. Mendel DB, et al. <u>In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Can</u> [3]. O'Farrell AM, et al. <u>SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood. 2003 May 1;101(9):3597-605. Epub 2003 Jan 16.</u>

源叶生物