



上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话: 021-61312973 传真: 021-55068248
网址: www.shyuanye.com
邮箱: shyysw@sina.com

产品名称: **SELEXIPAG**
产品别名: **NS-304; ACT-293987**

生物活性:

Description	Selexipag (NS-304) is an orally available and potent agonist for the Prostacyclin (PGI2) receptor (IP receptor).				
IC50 & Target	IP Receptor				
In Vitro	Selexipag (NS-304) is an orally available and long-acting IP receptor agonist prodrug, and its active form, MRE-269, is highly selective for the IP receptor. Selexipag (NS-304) inhibits the binding of [³ H]Iloprost to the human and rat IP receptors in a concentration-dependent manner. The K _i is 260 nM for the human IP receptor and 2100 nM for the rat IP receptor. The intracellular cAMP levels in hIP-CHO cells are increased in a concentration-dependent manner by treatment with Selexipag (NS-304) with EC ₅₀ of 177nM. Selexipag (NS-304) also inhibits platelet aggregation in humans and monkeys with IC ₅₀ values of 5.5 and 3.4 μM, respectively, but it shows no inhibition in dogs (IC ₅₀ of >100 μM)[1].				
In Vivo	The C _{max} of MRE-269 after oral administration of NS-304 is 1.1 μg/mL in rats and 9.0 μg/mL in dogs. Selexipag (NS-304) at 1 or 3 mg/kg increases FSBF in anesthetized rats for more than 4 h after intraduodenal administration in a dose-dependent manner. In particular, Selexipag (NS-304) at 3 mg/kg causes a sustained increase in FSBF and exhibits a maximal increase of 93% in FSBF 1 h after administration[1].				
Solvent&Solubility	In Vitro: DMSO : ≥ 50 mg/mL (100.68 mM) H₂O : < 0.1 mg/mL (insoluble) * "≥" means soluble, but saturation unknown.				
		Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	Preparing	1 mM	2.0136 mL	10.0681 mL	20.1361 mL
	Stock Solutions	5 mM	0.4027 mL	2.0136 mL	4.0272 mL
		10 mM	0.2014 mL	1.0068 mL	2.0136 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 (5.03 mM); Clear solution					
此方案可获得 ≥ 2.5 mg/mL (5.03 mM, 饱和度未知) 的澄清溶液。					



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	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 $\rightarrow$ 90% (20% SBE-β-CD in saline) Solubility: 2.5 mg/mL (5.03 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (5.03 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 $\rightarrow$ 90% corn oil Solubility: $\geq$ 2.5 mg/mL (5.03 mM); Clear solution 此方案可获得 $\geq$ 2.5 mg/mL (5.03 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]. Kuwano K, et al. 2-[4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy]-N-(methylsulfonyl)acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug. J Pharmacol Exp Ther. 2007 Sep;322(3):1181-8. [2]. Mous DS, et al. Treatment of rat congenital diaphragmatic hernia with sildenafil and NS-304, selexipag's active compound, at the pseudoglandular stage improves lung vasculature. Am J Physiol Lung Cell Mol Physiol. 2018 May 10.
实验参考:	
Cell Assay	CHO cells expressing the human IP receptor (hIP-CHO cells) are seeded at 1×10^5 cells/well in a 24-well plate and cultured for 48 h. The cells are washed with Dulbecco's phosphate-buffered saline without divalent cations, preincubated in the medium for 1 h at 37°C, and then incubated for 15 min at 37°C with medium containing each drug in the presence of 500 μM 3-isobutyl-1-methylxanthine. The medium is removed, and perchloric acid solution is added to terminate the reaction. Intracellular cAMP levels are measured by enzymelinked immunosorbent assay[1].
Animal Administration	Mice[1] Male Sprague-Dawley rats, cynomolgus monkeys, and male beagle dogs are used. Selexipag (NS-304) is orally administered to rats at 10 mg/kg and to dogs at 3 mg/kg, and blood samples are collected at various times and centrifuged to obtain plasma. The plasma concentrations of Selexipag (NS-304) and MRE-269 after oral administration of Selexipag (NS-304) to each animal are determined by high performance liquid chromatography coupled to mass spectrometry (LC/MS), and their pharmacokinetic parameters are calculated. Rats are orally administered Selexipag (NS-304) at 3 mg/kg twice daily for 1, 2, 3, or 4 weeks as a pretreatment. On the day after the final administration in the pretreatment, rats are anesthetized with urethane, and the FSBF is measured with a laser Doppler flowmeter after intraduodenal administration of Selexipag (NS-304) at 3 mg/kg[1].
	[1]. Kuwano K, et al. 2-[4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy]-N-(methylsulfonyl)acetamide (NS-304), an



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