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产品名称：Orteronel
产品别名：TAK-700

生物活性：

Description	Orteronel is a highly selective inhibitor of human 17,20-lyase with IC50 of 38 nM, and exhibits >1000-fold selectivity over other CYPs such as 11-hydroxylase and CYP3A4.
IC_{50} & Target	IC50: 38 nM (human 17,20-lyase), 54 nM (rat 17,20-lyase)
In Vitro	In monkey adrenal cells, orteronel inhibits the ACTH stimulated production of DHEA and androstenedione with IC50 of 110 nM and 130 nM, respectively. Moreover, Orteronel also potently inhibits DHEA production in human adrenocortical tumor line H295R cells with IC50 of 37 nM[1]. In vitro, orteronel shows the potent inhibitory activity against rat and human steroid 17,20-lyase with IC50 of 54 nM and 38 nM, respectively. While other CYP isoforms including 11-hydroxylase and CYP3A4 are not significantly affected by Orteronel. In microsomes expressing human CYP isoforms, Orteronel exhibit greater inhibitory effects on 17,20-lyase with IC50 of 19 nM compared to the other CYP isoforms[2].
In Vivo	Orteronel (1 mg/kg, p.o.) results in favorable pharmacokinetic parameters with Tmax, Cmax, t1/2 and AUC0-24 hours of 1.7 hours, 0.147 μg/mL, 3.8 hours and 0.727 μg/mL, respectively[1]. In cynomolgus monkeys, oral treatment of Orteronel at a dose of 1 mg/kg markedly reduces serum testosterone and dehydroepiandrosterone (DHEA) levels[2].

Solvent&Solubility

In Vitro:

DMSO : 14.29 mg/mL (46.49 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.2536 mL	16.2681 mL	32.5362 mL
	5 mM	0.6507 mL	3.2536 mL	6.5072 mL
	10 mM	0.3254 mL	1.6268 mL	3.2536 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: ≥ 1.43 mg/mL (4.65 mM); Clear solution

此方案可获得 ≥ 1.43 mg/mL (4.65 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 14.299999 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: ≥ 1.43 mg/mL (4.65 mM); Clear solution 此方案可获得 ≥ 1.43 mg/mL (4.65 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 14.299999 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: ≥ 1.43 mg/mL (4.65 mM); Clear solution 此方案可获得 ≥ 1.43 mg/mL (4.65 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 14.299999 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Yamaoka M, et al. Orteronel (TAK-700), a novel non-steroidal 17,20-lyase inhibitor: effects on steroid synthesis in human and monkey adrenal cells and serum steroid levels in cynomolgus monkeys. J Steroid Biochem Mol Biol. 2012 Apr;129(3-5):115-28. [2]. Kaku, Tomohiro., et al. Discovery of orteronel (TAK-700), a naphthylmethylimidazole derivative, as a highly selective 17,20-lyase inhibitor with potential utility in the treatment of prostate cancer. From Bioorganic & Medicinal Chemistry (2011), 19(21), 6

实验参考：

Animal Administration	Adult male cynomolgus monkeys housed in a temperature-controlled room (23±2°C) with a 12:12 h light/dark cycle (illumination from 7:00 am to 7:00 pm) are used for the single dosing experiments. The test compounds (+)-Orteronel and (−)-Orteronel are suspended in 0.5% methylcellulose and administered orally at a dose of 1 mg/kg. Blood samples are collected just before dosing and 8 h (in a preliminary study) or 2, 5 and 10 h after dosing. Serum is stored at −30°C until assayed by radioimmunoassay. Concentrations of testosterone and DHEA are determined using a Testosterone I-125 kit and a DHEA RIA kit, respectively. [2]
Kinase Assay	Rat 11-hydroxylase activity is measured according to a method described for side-chain cleavage activity previously with some modifications. The reaction mixture contained 200 mM mannitol, 4.5 mM HEPES, 2.3 mM potassium phosphate (pH 7.4), 0.1 mM EDTA·2 K, 0.03% BSA (crystallized), 4.5 mM NADPH, 11 mM calcium chloride, 4 μg of mitochondria protein, 10 nM [1,2-3H]-hydroxy-11-deoxycorticosterone (11-deoxycortisol) (NEN, dissolved in 0.02% Tween-80), and 1-1000 nM test compounds in a total volume of 150 μL. The concentrations of reagents are expressed as the final concentration in the reaction mixture. The test compounds are serially diluted with dimethylformamide, and 1.5 μL is added directly to the reaction mixture. After 30 min incubation at 37°C the reaction is terminated by addition of 400 μL of ethyl acetate and 100 μL of distilled water, then vortexed for 30 s and briefly centrifuged. Three hundred μLs of the organic phase is transferred to a new tube and evaporated until dry using nitrogen gas. The steroids are dissolved with 30 μL of ethyl acetate and the whole volume is applied to silica gel TLC plates. The substrate and the products (11-deoxycortisol and cortisol) are separated in the toluene-acetone (7:2) solvent system. [2]

References	[1]. Yamaoka M, et al. Orteronel (TAK-700), a novel non-steroidal 17,20-lyase inhibitor: effects on steroid synthesis in human and monkey adrenal cells and serum steroid levels in cynomolgus monkeys. J Steroid Biochem Mol Biol. 2012 Apr;129(3-5):115-28. [2]. Kaku, Tomohiro., et al. Discovery of orteronel (TAK-700), a naphthylmethylimidazole derivative, as a highly selective 17,20-lyase inhibitor with potential utility in the treatment of prostate cancer. From Bioorganic & Medicinal Chemistry (2011), 19(21), 6