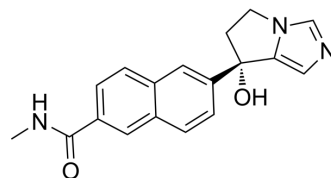


Orteronel

Cat. No.:	HY-10505		
CAS No.:	566939-85-3		
Molecular Formula:	C ₁₈ H ₁₇ N ₃ O ₂		
Molecular Weight:	307.35		
Target:	Cytochrome P450		
Pathway:	Metabolic Enzyme/Protease		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	2 years
		-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (81.34 mM; Need ultrasonic)

Concentration	Solvent	Mass		
		1 mg	5 mg	10 mg
Preparing Stock Solutions	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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
Solubility: ≥ 1.43 mg/mL (4.65 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: ≥ 1.43 mg/mL (4.65 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 1.43 mg/mL (4.65 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Orteronel (TAK-700) is a highly selective inhibitor of human 17,20-lyase (CYP17) with IC₅₀ of 38 nM, and exhibits >1000-fold selectivity over other CYPs such as 11-hydroxylase and CYP3A4^{[1][2]}.

IC₅₀ & Target

CYP17

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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Orteronel (1 mg/kg, p.o.) results in favorable pharmacokinetic parameters with T_{max}, C_{max}, t_{1/2} 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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay ^[2]

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.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Administration ^[2]

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.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Rep. 2016 Aug 26;6:32198.
- Prostate. 2017 Dec;77(16):1550-1562.

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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

Caution: Product has not been fully validated for medical applications. For research use only.

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