

Product Data Sheet

Product Name: Orteronel

Cat. No.: GC16886

Chemical Properties

Cas. No. 566939-85-3

Chemical Name 6-[(7S)-7-hydroxy-5,6-dihydropyrrolo[1,2-c]imidazol-7-yl]-N-methylnaphthalene-2-carboxamide

SMILES CNC(=O)c1ccc2cc(ccc2c1)[C@H]3C=CN4C(=CN=C4)C3

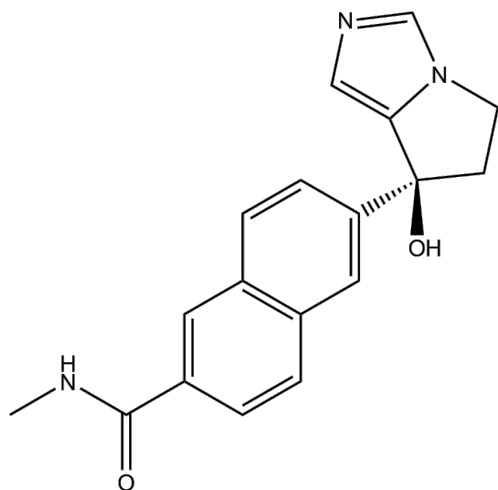
Formula $C_{18}H_{17}N_3O_2$ M.Wt 307.35

Solubility DMF: 10 mg/ml, DMSO: 10 mg/ml, Ethanol: 0.2 mg/ml Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

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

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**Kinase
experiment:**

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.

**Animal
experiment:**

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.

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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

Background

IC50: Orteronel inhibited monkey 17,20-lyase and 17-hydroxylase activities with IC50 values of 27 and 38 nmol/L, respectively [1].

Orteronel is an androgen biosynthesis inhibitor. It selectively inhibits the enzyme CYP17A1 which is expressed in testicular, adrenal, and prostatic tumor tissues. CYP17 catalyzes two sequential reactions: (a) the conversion of pregnenolone and progesterone to their 17 α -hydroxy derivatives by its 17 α -hydroxylase activity, and (b) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by its 17,20-lyase activity (<http://en.wikipedia.org/wiki/Orteronel>).

In vitro: Orteronel potently suppresses androgen production in monkey adrenal cells but only weakly suppresses corticosterone and aldosterone production; the IC50 value of orteronel for cortisol was about 3-fold higher than that for DHEA. Moreover, in human CYP17A1 and human adrenal tumor cells, orteronel inhibited 17,20-lyase activity 5.4 times more potently than 17-hydroxylase activity in cell-free enzyme assays and DHEA production 27 times more potently than cortisol production in human adrenal tumor cells, suggesting greater specificity of inhibition between 17,20-lyase and 17-hydroxylase activities in humans vs monkeys [1].

In vivo: After Orteronel single oral dosing, serum levels of DHEA, cortisol, and testosterone were rapidly suppressed in intact cynomolgus monkeys. In castrated monkeys treated twice daily with orteronel, suppression of DHEA and testosterone persisted throughout the treatment period. These findings suggest that orteronel may be an effective therapeutic option for diseases where androgen suppression is critical, such as androgen sensitive and CRPC [1].

Clinical trial: Takeda Pharmaceutical Company Limited announced that it has voluntarily decided to

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end the development program for orteronel (TAK-700) for prostate cancer. The decision follows the results of two Phase 3 clinical trials in metastatic, castration resistant prostate cancer (mCRPC). The studies found while orteronel plus prednisone could extend the time patients lived before their cancer progressed, it did not extend overall survival in these patients. After careful consideration of the data from these trials, the company has determined that the drug has not demonstrated a clinical profile sufficient to move forward in mCRPC, given the availability of other therapies.

Reference:

[1] Yamaoka M, Hara T, Hitaka T, Kaku T, Takeuchi T, Takahashi J, Asahi S, Miki H, Tasaka A, Kusaka M. 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;129(3-5):115-28.

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