

Product Data Sheet

Product Name: Voriconazole

Cat. No.: GC13079

Chemical Properties

Cas. No. 137234-62-9

Chemical Name (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol

SMILES CC(C1=NC=NC=C1F)C(CN2C=NC=N2)(C3=C(C=C(C=C3)F)F)O

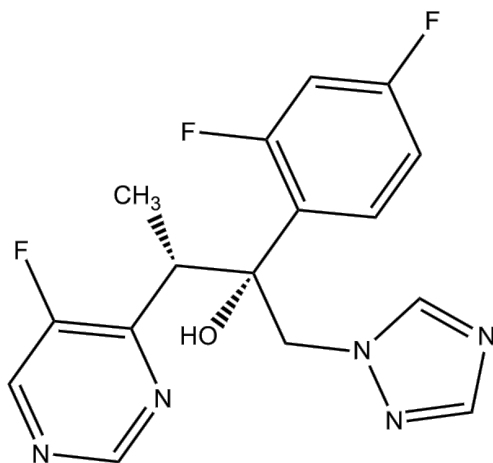
Formula $C_{16}H_{14}F_3N_5O$ M.Wt 349.31

Solubility ≥ 34.9 mg/mL in DMSO, ≥ 45 mg/mL in EtOH with ultrasonic and warming 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

Cell experiment [1]:

Cell lines Human corneal endothelial cells

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

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Human corneal endothelial cells (5×10^4 cells/ml) were grown in 96-well plates for 48 hours and treated with different concentrations (0, 5, 25, 50, 100, 250, 500, and 1000 µg/ml) of Voriconazole. After 24 hours, human corneal endothelial cells were washed and the degree of cell growth was evaluated using CCK-8 assay, absorbance at 450nm was measured using a microplate reader.

Reaction Conditions 0, 5, 25, 50, 100, 250, 500, and 1000 µg/ml; 24h

Applications Voriconazole treatment significantly inhibited the cell viability at the concentration ≥ 100 µg/ml.

Animal experiment [2]:

Animal models BALB/cByJ mice

Male BALB/cByJ mice were allowed to freely consume mouse food and water. Five days before infection, the water in the water bottles was replaced with grapefruit juice and the mice were allowed to drink freely. The mice consumed an average of 2 to 3ml of grapefruit juice per day. The mice were lightly anesthetized with fentanyl. Approximately 5×10^4 CFU of *B. dermatitidis* yeasts/0.05ml solution was placed in the nostrils of the mice, and the mice remained in a standing position. After inhaling the droplets, the mice were returned to the cage. Ten mice were used in each group for survival rate determination. Voriconazole treatment was initiated 5 days after infection and continued for 21 days. Voriconazole was administered orally by gavage at a dose of 40mg/kg/day. The mice were observed twice a day, and the death situation was recorded. The experiment ended on the 45th day, and the mice were sacrificed, the lungs were removed and homogenized for processing. The cultures were inoculated on glucose agar plates at an appropriate dilution and incubated at 37°C for 5 days before counting the colony numbers.

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Dosage form 40mg/kg/day for 21 days; p.o.

Applications Voriconazole treatment increased the survival rate of mice and reduced the fungal burden in the lungs.

References:

- [1] Han S B, Shin Y J, Hyon J Y, et al. Cytotoxicity of voriconazole on cultured human corneal endothelial cells[J]. *Antimicrobial Agents and Chemotherapy*, 2011, 55(10): 4519-4523.
- [2] Sugar A M, Liu X P. Efficacy of voriconazole in treatment of murine pulmonary blastomycosis[J]. *Antimicrobial agents and chemotherapy*, 2001, 45(2): 601-604.

Background

Voriconazole is a potent competitive inhibitor of CYP2B6 ($IC_{50}=1.71\mu M$), CYP2C9 ($IC_{50}=3.62\mu M$), CYP2C19 ($IC_{50}=5.25\mu M$), and CYP3A ($IC_{50}=2.90\mu M$)^[1]. Voriconazole inhibited AfCYP51A and AfCYP51B activities in recombinant *Aspergillus fumigatus* with IC_{50} values of $0.38\mu M$ and $0.33\mu M$, respectively, leading to inhibition of ergosterol biosynthesis^[2]. Voriconazole has potent activity against a variety of clinically important fungal pathogens, including *Aspergillus*, *Candida*, *Cryptococcus neoformans*, and some less common moulds^[3].

In vitro, Voriconazole treatment for 48h significantly inhibited 102 clinical *Candida species* and *Saccharomyces cerevisiae* isolates with $MIC_{50}\leq 0.125\mu g/mL$ ^[4]. At a concentration of $1000\mu g/mL$, Voriconazole significantly reduced the cell viability of human corneal endothelial cells, altered the morphological characteristics, and significantly activated the apoptotic pathway^[5]. At a concentration of $135\mu M$, Voriconazole treatment for 7 days in primary human keratinocytes (PHK) upregulated genes related to cell division, chromosome condensation, DNA replication, spindle organization, and cell cycle checkpoint control, and downregulated genes related to terminal epithelial differentiation and protease inhibitor activity^[6].

In vivo, Voriconazole treatment via intravenous administration (40mg/kg plus grapefruit gavage twice daily) for 7 days, the renal and brain burdens of mice infected with *Candida tropicalis* were

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alleviated^[7]. Oral administration of Voriconazole (40mg/kg) daily for 21 days significantly reduced the fungal burden in the lungs of BALB/cByJ mice, increased the survival rate, and alleviated murine pulmonary blastomycosis^[8].

References:

- [1] Jeong S, Nguyen P D, Desta Z. Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: major effect on CYPs 2B6, 2C9, 2C19, and 3A[J]. Antimicrobial agents and chemotherapy, 2009, 53(2): 541-551.
- [2] Warrilow A G S, Parker J E, Price C L, et al. Isavuconazole and voriconazole inhibition of sterol 14 α -demethylases (CYP51) from *Aspergillus fumigatus* and *Homo sapiens*[J]. International Journal of Antimicrobial Agents, 2019, 54(4): 449-455.
- [3] Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole[J]. Clinical pharmacokinetics, 2006, 45(7): 649-663.
- [4] Chryssanthou E, Cuenca-Estrella M. Comparison of the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antibiotic Susceptibility Testing proposed standard and the E-test with the NCCLS broth microdilution method for voriconazole and caspofungin susceptibility testing of yeast species[J]. Journal of clinical microbiology, 2002, 40(10): 3841-3844.
- [5] Han S B, Shin Y J, Hyon J Y, et al. Cytotoxicity of voriconazole on cultured human corneal endothelial cells[J]. Antimicrobial Agents and Chemotherapy, 2011, 55(10): 4519-4523.
- [6] Mansh M, Ing L, Dimon M, et al. Voriconazole exposure regulates distinct cell-cycle and terminal differentiation pathways in primary human keratinocytes[J]. British Journal of Dermatology, 2017, 176(3): 816-820.
- [7] Majithiya J, Sharp A, Parmar A, et al. Efficacy of isavuconazole, voriconazole and fluconazole in temporarily neutropenic murine models of disseminated *Candida tropicalis* and *Candida krusei*[J]. Journal of Antimicrobial Chemotherapy, 2009, 63(1): 161-166.
- [8] Sugar A M, Liu X P. Efficacy of voriconazole in treatment of murine pulmonary blastomycosis[J]. Antimicrobial agents and chemotherapy, 2001, 45(2): 601-604.

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