Posaconazole
PRODUCT DATA SHEET

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Product Name:	Posaconazole
Product Number:	P139
CAS Number:	171228-49-2
Molecular Formula:	$C_{37}H_{42}F_2N_8O_4$
Molecular Weight:	700.78
Form:	Powder
Appearance:	White to off-white crystalline powder
Solubility:	Slightly soluble in DMSO. Practically insoluble in water.
Source:	Synthetic
Storage Conditions:	-20°C
Description:	Posaconazole is a synthetic, broad-spectrum, second generation triazole with antifungal activity. It has potent *in vitro* and *in vivo* trypanocidal activity. It was discovered by Schering-Plough and it is a structural analog of itraconazole. The compound has promising anti-cancer properties. Posaconazole is slightly soluble in DMSO but is practically insoluble in water.
Mechanism of Action:	Posaconazole blocks ergosterol synthesis, by inhibiting the enzyme lanosterol 14 α-demethylase. The result is an accumulation of methylated sterol precursors. It also inhibits CYP3A4, but does not inhibit the activity of other CYP enzymes thus it may have the potential for fewer drug interactions.
Spectrum:	Broad-spectrum antifungal activity including yeast (*Candida*) and fungi (*Aspergillus*, *Scedosporium*, *Fusarium*, *Zygomycetes*). It is effective against the parasite *Trypanosoma cruzi,* the causal agent of Chagas disease. Triazole resistance is increasing among fungal pathogens including *Candida* spp. due to multiple molecular mechanisms.

Microbiology Applications

Posaconazole was involved in a 10-year study of 19,000 clinically important strains of yeast and mold with 200 medical centers participating. Strains were tested using CLSI broth microdilution methods with RPMI 1640 medium, with MIC_{50} (0.063 ug/ml) and MIC_{90} (1 µg/ml) for all fungal isolates in the database. . For both yeasts and molds, MIC_{90} was 1 µg/ml. The compound was active against *Candida* and *Aspergillus* isolates that are resistant to Fluconazole, Voriconazole, and Amphotericin B (Sabatelli et al, 2006).

The *in vivo* efficacy of Poscanazole was studied in a murine model against 4 *Aspergillus fumigatus* isolates with MICs values of 0.03-16 mg/L. Resistance mechanisms included substitutions in the *cyp51A* gene. (Mavridou et al, 2010).

As a trypanocidal agent, it can act synergistically with Amiodarone. It disrupts $Ca2^{+}$ homeostasis in *T. cruzi* (Benaim et al, 2006). The antiproliferative synergism of the compounds was characterized using electron microscopy (Veiga-Santos P et al, 2012) and this association is promising against *T. cruzi.*

Cancer Applications

Deregulation of the Hedgehog (Hh) pathway signaling pathway, a highly conserved developmental pathway, leads to disorders and cancers such as basal cell carcinoma. Under normal conditions, binding of a Hh ligand, relieves its inhibition of Smoothened (SMO), a transmembranae protein. Posaconazole inhibits the Hh pathway that by a similar mechanism to itraconazole. It is a promising compound for Hh-dependent cancers (Chen B et al, 2016).

References:

Benaim G et al (2006) Amiodarone has intrinsic anti-*Trypanosoma cruzi* activity and acts synergistically with Posaconazole. J. Med. Chem. 49(3):892-899 PMID 16451055

Chen CK (2010) Structural characterization of CYP51 from Trypanosoma cruzi and Trypanosoma brucei bound to the antifungal drugs Posaconazole and fluconazole. PLoS Negl Trop Dis. 4(4):e651 PMID 20386598

Chen B et al (2016) Posaconazole, a second-generation triazole antifungal drug, inhibits the hedgehog signaling pathway and progression of basal cell carcinoma. Mol Cancer Ther . 15(5):866-876

Harbrecht R (2004) Posconazole: A potent, extended-spectrum triazole anti-fungal for the treatment of serious fungal infections. Int. J. Clin. Pract. 58(6):612-624

Mavridou E, Brüggemann RJ, Melchers WJ, Mouton JW, Verweij PE (2010) Efficacy of Posaconazole against three clinical *Aspergillus fumigatus* isolates with mutations in the cyp51A gene. Antimicrob. Agents Chemother. 54(2):860-865 PMID 19917751

Nomeir AA et al (2008) Posaconazole (Noxafil, SCH 56592), a new azole antifungal drug, was a discovery based on the isolation and mass spectral characterization of a circulating metabolite of an earlier lead (SCH 51048). J Mass Spectrom. 43(4):509-517 PMID 18059003

Sabatelli F et al (2006) *In vitro* activities of Posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. Antimicrob. Agents Chemother. 50(6):2009-2015 PMID 16723559

Veiga-Santos P et al (2012) Effects of amiodarone and Posaconazole on the growth and ultrastructure of *Trypanosoma cruzi*. Int. J. Antimicrob. Agents 40(1):61-71 PMID 22591838