Anti-fungal activity of PC1244, a novel azole, on azole sensitive and resistant Aspergillus fumigatus strains and other fungi

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Introduction

PC1244 is a novel antifungal agent designed for inhalation treatment of invasive aspergillosis or difficult fungi. In this study, the in vitro profile of PC1244 was investigated against Aspergillus fumigatus (A. fumigatus) and a range of yeasts and moulds.

Methods

CYP51A and CYP51B binding affinity and enzyme inhibition were determined using recombinant A. fumigatus CYP51A/B. Anti-fungal potency was evaluated using the EUCAST broth microdilution method by visual inspection and using optical density (OD) measurements to quantify growth. Anti-fungal potency against an extended range of fungi were evaluated using OLSI broth microdilution in Eurofins-Panlabs.

Results

PC1244 targets A.fumigatus CYP51

PC1244 has a high affinity for both A. fumigatus CYP51A and CYP51B proteins, and was a strong tight binding inhibitor of CYP51A/B enzyme activity. PC1244 also showed the depletion of ergosterol content in A. fumigatus membranes with the characteristic accumulation of 14-methylated sterols (lanosterol/obtusifoliol and eburicol). Figure 1. Inhibitory activity of PC1244 (O) and posaconazole (●) against CYP51A/B

Table 1. Inhibitory activities and binding properties of PC1244 and posaconazole

Table 2. Effects of PC1244 and posaconazole on sterol composition of A.fumigatus

PC1244 inhibits growth of azole sensitive and azole resistant A.fumigatus

In broth microdilution assays, PC1244 was a potent and highly effective inhibitor of growth of A.fumigatus-itraconazole susceptible strains (NCFP2010 and AF93) with MIC<sub>90</sub> (90% inhibition of growth determined by OD) of 0.0022 µg/mL and 0.012 µg/mL, respectively. PC1244 also showed more potent inhibition of growth of A.fumigatus-itraconazole resistant strains (AF91 (M220V), AF72 (G54E), TR34-L98H (Paris) and TR46-Y1121/T289A (India)) than voriconazole or posaconazole, with MIC<sub>90</sub> of 0.024 µg/mL, 0.026 µg/mL, 0.024 µg/mL, 0.17 µg/mL, respectively. Table 3. Anti-fungal effects of PC1244 and reference compounds

Figure 2. MIC distribution of clinically isolated A.fumigatus from St Louis hospital.

Figure 3. MIC distribution of clinically isolated A.fumigatus from North West England mycology reference centre

Anti-fungal effects of PC1244 and posaconazole in other fungal species

Table 4. Anti-fungal effects against other fungal species

In a panel against an extended range of fungi, PC1244 was found to be a potent inhibitor on other Aspergillus spp. (flavus, carbonarius, pullulans), Rhizopus oryzae, Cryptococcus neoformans, Chlamydomonas globosum, Cladosporium argillaceum, Penicillium chrysogenum, Penicillium citrinum, Fusarium graminearum, Trichophyton rubrum, Candida albicans, Candida glabrata, Candida krusei and Candida tropicalis (MIC range: 0.0031 – 1 µg/mL).

Conclusion

In this study, PC1244 was shown to be a potent A. fumigatus CYP51 inhibitor and demonstrated more potent activity against several strains of A. fumigatus, including those with well characterised CYP51A mutations, and clinical isolates. We also found beneficial effects of PC1244 on several yeast and filamentous fungi. PC1244 therefore has the potential to be a novel therapy for the treatment of A. fumigatus and other difficult fungi infections in humans.