Anti-fungal activities of PC1244, a novel inhaled triazole, on *Aspergillus fumigatus* strains with *cyp51A* mutations

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Introduction

PC1244 is a novel potent and long acting antifungal triazole designed for inhalation treatment of pulmonary aspergillosis and other difficult to treat fungi. In this study the antifungal activities of PC1244 were assessed by performing susceptibility testing against well-characterized azole-resistant *Aspergillus fumigatus* isolates.

Methods

In-vitro antifungal susceptibility of PC1244 (0.016 – 8 µg/ml) was tested, in comparison with voriconazole (0.031 – 16 µg/ml) and posaconazole (0.016 – 8 µg/ml), against TR_{34}/L98H (n=36), TR_{46}/Y121F/T289A (n=12), M220 (n=6), G54 (n=5), TR_{92}/ Y121F/T289A (n=1), G432C (n=1) and P216S (n=1) *A. fumigatus* mutants originated from India and the Netherlands using CLSI broth microdilution. The antifungal susceptibility data obtained were further compared with MIC values of wild-type *A. fumigatus* strains (n=3), including a quality control strain (ATCC204305). Antifungal drugs were dissolved in DMSO and applied to wells in microdilution plates at a final concentration of 1% DMSO.

Results

PC1244 background

PC1244, 4-(4-(4-(((3*R*,5*R*)-5-((1*H*-1,2,4-triazol-1-yl)methyl)-5-(2,4-difluorophenyl)tetrahydrofuran-3-yl)methoxy)-3-methylphenyl)piperazin-1-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclohexyl) benzamide (Figure 1) is a potent triazole anti-fungal agent, which is *superior to Voriconazole and comparable to Posaconazole against Aspergillus fumigatus clinical isolates (Figure 2), and it has been designed to have physicochemical properties suitable for topical administration to the lung and promote long lasting tissue residency (AAA16, Manchester).*

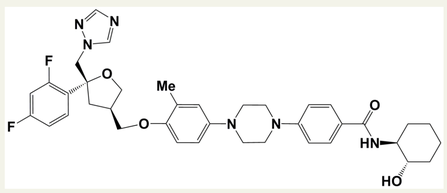

Figure 1. Structure of PC1244

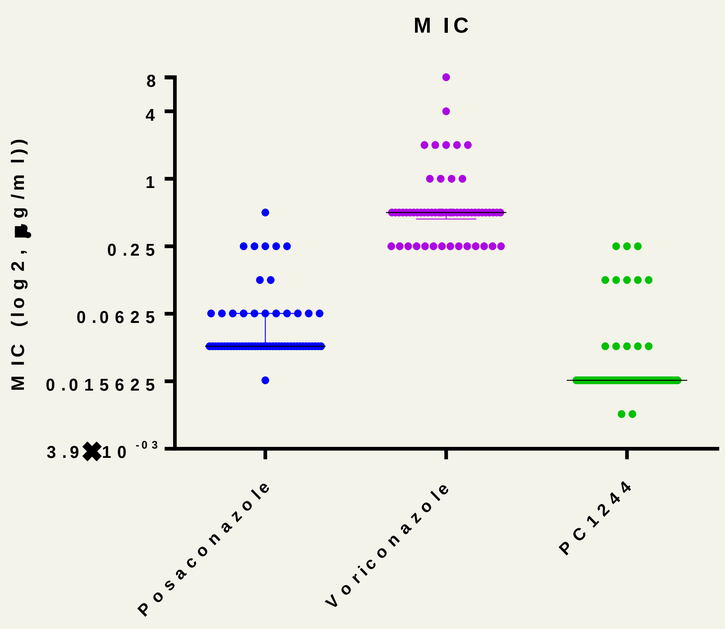

Figure 2. MIC distribution of 58 clinically isolated *A.fumigatus* from St Louis hospital.

PC1244 inhibits growth of wild type and CYP51A mutated *A.fumigatus*

The MIC values of voriconazole and posaconazole against quality control ATCC204305 were 1 µg/mL and 0.25 µg/mL, respectively, and that of PC1244 was 0.25 µg/mL. The median MIC values of PC1244 against TR_{34}/L98H, TR_{46}/Y121F/T289A, G54, M220 and wild type were 1 µg/mL, 1 µg/mL, 1 µg/mL, 1 µg/mL and 0.25 µg/mL, respectively. PC1244 was much more potent than voriconazole and comparable to posaconazole (Table 1 and Figure 3). Single mutant isolates carrying TR_{92}/ Y121F/T289A, G432C and P216S mutations exhibited MIC values of 1 µg/mL, 1 µg/mL and 0.5 µg/mL for PC1244, >16 µg/mL, >16 µg/mL and 1 µg/mL for voriconazole and 1 µg/mL, 1 µg/mL and 0.5 µg/mL for posaconazole (Table 1).

Overall, the geometric mean MIC [median, range] of 59 isolates was 0.92 µg/mL [1, 0.125->8] for PC1244, 16 µg/mL [16, 0.5->16] for voriconazole and 1.1 µg/mL [1, 0.5->8] for posaconazole.

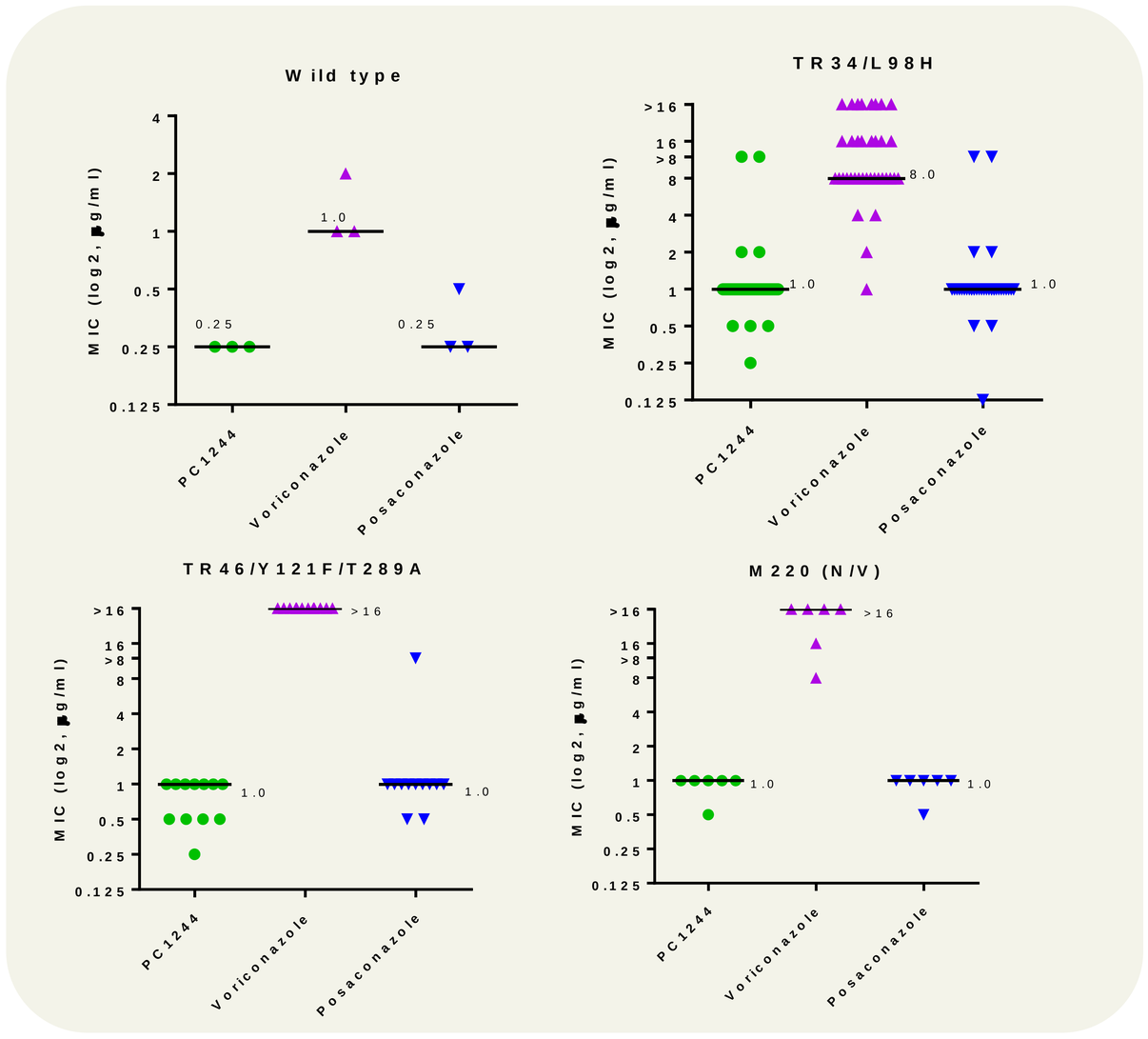

Figure 3. MIC distribution of *A.fumigatus strains with cyp51A mutations*

Table 1. Median MIC values of PC1244 and reference compounds against ASP mutants

		Median MIC (µg/mL)		
mutation	**(n)**	**PC1244**	**Voriconazole**	**Posaconazole**
Wild type	3	0.25	1	0.25
TR34/L98H	36	1	8	1
TR46/Y121F/T289A	12	1	>16	1
G54	5	1	1	1
M220	6	1	>16	1
TR92/Y121F/T289A	1	1	>16	1
G432C	1	1	>16	1
P216S	1	0.5	1	0.5

Conclusion

PC1244 demonstrated more potent activities against *A. fumigatus* with well characterised *cyp51A* mutations than voriconazole. PC1244, therefore, has the potential to become a novel approach for the topical treatment of pulmonary aspergillosis.

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