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In vitro antifungal activity of a novel topical triazole PC945 against emerging yeast *Candida auris*

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Objectives: Management of *Candida auris* infection is difficult as this yeast exhibits resistance to different classes of antifungals, necessitating the development of new antifungals. The aim of this study was to investigate the susceptibility of *C. auris* to a novel antifungal triazole, PC945, optimized for topical delivery.

Methods: A collection of 50 clinical isolates was obtained from a tertiary care hospital in North India. Nine isolates from the UK, 10 from a CDC panel (USA) and 3 from the CBS-KNAW culture collection (Japanese and South Korean isolates) were also obtained. MICs (azole endpoint) of PC945 and other triazoles were determined in accordance with CLSI M27 (third edition). Quality control strains were included [*Candida parapsilosis* (ATCC 22019) and *Candida krusei* (ATCC 6258)].

Results: Seventy-four percent of isolates tested showed reduced susceptibility to fluconazole ($\geq$64 mg/L). PC945 (geometric mean MIC=0.058 mg/L) was 7.4-fold and 1.5-fold more potent than voriconazole and posaconazole, respectively (both $P<0.01$). PC945 MIC values correlated with those of voriconazole or posaconazole, and only three isolates were found to be cross-resistant between PC945 and other azoles. *ERG11* sequence analysis revealed several mutations, but no correlation could be established with the MIC of PC945. Tentative epidemiological cut-off values (ECOFFs) evaluated by CLSI's ECOFF Finder (at 99%) with 24 h reading of MICs were 1, 4 and 1 mg/L for PC945, voriconazole and posaconazole, respectively. MIC values for quality control strains of all triazoles were in the normal ranges.

Conclusions: PC945 was found to be a more potent inhibitor than posaconazole, voriconazole and fluconazole of *C. auris* isolates collected globally, warranting further laboratory and clinical evaluations.

Introduction

Candida auris was first isolated in 2009[1,2] and has been increasingly reported from far-Eastern Asia, the Middle East, Africa, Europe, North America and South America.[3] It is considered to be an emerging yeast and expected to pose a serious global health threat due to its MDR nature, causing invasive infection with high mortality. According to the recent meta-analysis,[3] 44.29% of *C. auris* are resistant to fluconazole, 15.46% to amphotericin B and 12.67% to voriconazole. Thus, the lower susceptibility of *C. auris* to current antifungals limits treatment options.

The majority of cases have been identified as secondary nosocomial infections. In a large multicentre study on ICU-acquired candidaemia in India, *C. auris* was isolated in 5.3% of 1400 candidaemia cases.[4] It has the potential to transmit easily between patients and hospitals. Longer stay in ICU, underlying respiratory illness, vascular surgery, medical interventions and antifungal exposure are the major risk factors for acquiring *C. auris* infection in ICU settings.[5] This yeast has been shown to persist in the hospital environment. Although *C. auris* was originally isolated from an ear and also from a range of body sites, including skin and urogenital tract, so far, no single point source of transmission has been identified. *C. auris* has also been isolated from sputum[6,7] and bronchoalveolar lavage fluid (BALF)[8–10] samples, and from the nasal cavity[11] and hands[12] of healthcare workers in hospitals in the UK and India. In addition, the first clinical case of donor-derived *C. auris* transmission in a lung transplant recipient has been reported recently.[10]

PC945, 4-[4-(4-{[(3R, 5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)oxolan-3-yl]methoxy}-3-methylphenyl) piperazin-1-yl]-N-(4-fluorophenyl) benzamide, is a novel antifungal triazole that has been shown to have potent antifungal activity on itraconazole-susceptible and -resistant *Aspergillus fumigatus* isolates with inhibition of the enzyme lanosterol 14α-demethylase (CYP51A1).[13] In addition, PC945 has demonstrated potent activity against standard *Candida albicans* and *Candida glabrata*.[13] PC945 has been designed for topical delivery to achieve high local concentrations with retention in cells, offering a long duration of action.[13] It has also been shown to result in minimal systemic exposure by poor oral availability and high protein plasma binding, leading to minimal potential systemic side effects.

Thus, the aim of this study was to evaluate the antifungal effects of PC945 and compare with the triazoles fluconazole, posaconazole and voriconazole against *C. auris* isolates from India, the UK, the USA (CDC collection) and East Asia.

Materials and methods

Antifungal agents

PC945 was synthesized by Sygnature Discovery Ltd (Nottingham, UK), whereas voriconazole (Tokyo Chemical Industry UK Ltd, Oxford, UK), posaconazole (Apichem Chemical Technology Co., Ltd, Zhejiang, China), itraconazole (Arkopharma, Carros, France), fluconazole (Alfa Aesar, Heysham, UK) and amphotericin B (Selleckchem, Munich, Germany) were procured from commercial sources.

Strains

A collection of 50 clinical strains isolated from different hospitals across India, 3 isolates (Pakistani/Indian clade) obtained from the Royal Brompton Hospital (London, UK), 6 UK clinical isolates (South African clade)[7] from a collection of the National Collection of Pathogenic Fungi (NCPF, Bristol, UK; NCPF 8977, 8979, 8980, 8996, 13014 and 13042), 10 isolates obtained from the CDC/FDA Antibiotic Resistance Isolate Bank (Atlanta, GA, USA; https://www.cdc.gov/ARIsolateBank/Panel; AR Bank 0381, 0382, 0383, 0384, 0385, 0386, 0387, 0388, 0389 and 0390) and 3 isolates from a collection of the Westerdijk Fungal Biodiversity Centre [former CBS-KNAW Fungal Diversity Centre, Utrecht, The Netherlands; CBS10913 (isolated from a patient in Japan[2]), CBS12372 (South Korea[1]) and CBS12373 (South Korea[1])] were used in the study. *Candida parapsilosis* (ATCC 22019) and *Candida krusei* (ATCC 6258) were also used as control strains (ATCC, Manassas, VA, USA).

MIC determinations

Antifungal susceptibility testing of *C. auris* was performed in accordance with CLSI M27 (third edition).[14] As per the protocol, RPMI-1640 medium with 3-(N-morpholino) propanesulfonic acid (RPMI), an inoculum of 0.25–0.5×10^3 cells/mL and incubation at 35°C for 48 h were used. The results were read separately at 24 and 48 h after incubation. MIC endpoints were determined visually as the lowest concentration of compound that resulted in the complete inhibition of growth (amphotericin B, PC945) or a decrease of growth by ≥50% relative to that of the growth control (azole endpoint: PC945, itraconazole, posaconazole and/or voriconazole).[14] Stock solutions of test agents were prepared in neat DMSO and were diluted 100-fold to the desired concentrations with growth media, ensuring that DMSO was 1% (v/v) throughout all the assay plates. Broth microdilution assays for Indian isolates were performed at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, for UK isolates at Pulmocide Ltd (London, UK) and for the CDC/CBS panels at Evotec (UK) Ltd (Manchester, UK).

ERG11 gene amplification and sequencing

ERG11 gene sequence and analysis was conducted as previously published.[15] Briefly, PCR conditions included initial denaturation for 2 min at 94°C followed by 35 cycles of 30 s at 94°C, 30 s at 55°C and 120 s at 72°C with the amplification primers for *ERG11*, 5′-GTGCCCATCGTCTACAACCT-3′ (forward 1) and 5′-TCTCCCACTCGATTTCTGCT-3′ (reverse 1). Sanger DNA sequencing was performed in GeneWiz UK Ltd (Bishop's Stortford, UK) using the sequencing primers [5′-TGGGTKGGYTCWGCTGTTG-3′ (forward 2) and 5′-TTCWGCTGGYTCCATTGG-3′ (reverse 2)] at 10 μM concentration. Consensus sequences were aligned with a reference *C. auris ERG11* sequence (GenBank accession no. MK059959).

Statistical analysis

Statistical analyses of all the data were performed using the PRISM 6® software program (GraphPad Software Inc., San Diego, CA, USA) and the results are expressed as geometric mean (GM) MIC, MIC_{50} and MIC_{90}. Multiple comparison was performed by ANOVA followed by Tukey's multiple comparison test or by the Friedman test followed by Dunn's multiple comparison test. Statistical significance was defined as $P<0.05$. Epidemiological cut-off values (ECOFFs) were calculated using ECOFF Finder (https://clsi.org/meetings/microbiology/ecoffinder/).

Results

MICs for Indian C. auris isolates

The majority (39/50, 78%) of Indian isolates showed reduced susceptibility to fluconazole (MIC ≥ 64 mg/L) (Table S1, available as Supplementary data at *JAC* Online).

The GM MICs recorded after 24 h of incubation were 0.059, 0.44, 0.10 and 59 mg/L for PC945, voriconazole, posaconazole and fluconazole, respectively (Table 1 and Table S1). For 48 h reading, PC945 was 7–8-fold and 2-fold more potent than voriconazole and posaconazole, respectively, based on GM MIC and MIC_{90} values (Table 1 and Table S2), and the values were more or less similar to those recorded after 24 h of incubation. The GM MIC of PC945 was significantly lower than that of voriconazole and posaconazole. See Table 1.

MIC values of fluconazole, voriconazole and posaconazole for quality control strains [*C. krusei* (ATCC 6258) and *C. parapsilosis* (ATCC 22019)] were within the expected MIC ranges (Table S3). Furthermore, PC945 also demonstrated complete inhibition of fungal growth and the GM MIC and MIC_{90} values of complete inhibition (amphotericin B endpoint) were 0.16 and 0.5 mg/L, respectively (Table S1 and Table S2).

MICs for UK C. auris isolates

The nine UK isolates tested (three from the Pakistani/Indian clade and six belonging to the South African clade) showed high MICs (five out of nine MICs were ≥64 mg/L) of fluconazole 24 h after incubation (Table 1 and Table S4). Based on GM MIC values read at 24/48 h, PC945 was 6.3-/25-fold and 2.2-/2.3-fold more potent than voriconazole and posaconazole, respectively (Table 1, Table S4 and Table S5). MIC values of PC945 were significantly lower than those of voriconazole. MIC values of fluconazole, voriconazole and posaconazole for the quality control strain *C. parapsilosis*

Table 1. Susceptibility testing of all *C. auris* isolates to PC945 and other antifungal triazoles

	Isolates	No.	GM MIC (MIC_{50}, MIC_{90}), mg/L			
			PC945	VOR	POS	FLC
24 h reading	Indian	50	0.059 (0.063, 0.13)	0.44 (0.5, 1)[c]	0.10 (0.13, 0.25)[f]	59 (64, >64)
	UK[a]	9	0.015 (0.008, 0.3)	0.37 (0.5, >4)[c]	0.034 (0.016, >4)[e]	55 (64, >64)
	CDC/CBS[b]	13	0.15 (0.13, 0.5)	ND	ND	ND
	total	72	0.058 (0.063, 0.25)	0.43 (0.5, 1)[c,d]	0.088 (0.125, 0.25)[c,d]	>64 (64, >64)[d]
48 h reading	Indian	50	0.086 (0.13, 0.25)	0.66 (0.75, 2)[c]	0.18 (0.13, 0.5)[c]	>64 (>64, >64)
	UK[a]	9	0.63 (0.5, >4)	>4 (>4, >4)[e]	1.4 (>4, >4)[e]	>64 (>64, >64)
	CDC/CBS[b]	13	0.36 (0.25, 3.6)	1.2 (2, >4)[f]	0.34 (0.5, 0.9)[e]	ND
	total	72	0.14 (0.13, 1)	0.95 (1, >4)[c]	0.26 (0.25, 0.95)[f]	>64 (64, >64)[d]

AMB, amphotericin B; FLC, fluconazole; ND, not done; POS, posaconazole; VRC, voriconazole.
Assays were conducted in accordance with CLSI M27 (third edition) and plates were read after 24 or 48 h of incubation.
[a]Including three Pakistani/Indian clade isolates and six South African clade isolates.
[b]Including isolates from the CDC/FDA Antibiotic Resistance Isolate Bank and three from CBS-KNAW (details in Table 2).
[c]$P<0.01$ versus PC945.
[d]$n=59$.
[e]Not significant versus PC945.
[f]$P<0.05$ versus PC945.

(ATCC 22019) were within the expected MIC ranges (voriconazole, 0.031; posaconazole, 0.063; fluconazole, 1.0; amphotericin B, 0.25–0.5; and PC945, 0.016–0.031 mg/L).

MICs for C. auris in the CDC/CBS panels

A wide range of MIC variation was noted for amphotericin B for the CDC panel isolates and 7 out of 10 isolates showed low susceptibility to fluconazole (Table 2) according to CDC in-house data. Our assays for voriconazole and posaconazole produced similar MIC values to those reported by CDC (Table S7). PC945 (GM MIC=0.36 mg/L for 48 h reading) was 3.3-fold more potent than voriconazole and comparable to posaconazole (Table 2 and Table S7). The Japanese isolate in the CBS panel was more susceptible to PC945 than the Korean isolates (Table 2). The 24 h reading of PC945 showed good activity (GM MIC=0.15 mg/L) against all 13 of these isolates (Table S6). MIC values of voriconazole and posaconazole were in the prescribed ranges for the quality control strain *C. parapsilosis* (ATCC 22019) (0.25 and 0.03 mg/L, respectively).

Comparison of susceptibility testing of PC945 with triazoles

The majority (53/72, 74%) of isolates tested in this study showed reduced susceptibility to fluconazole (≥64 mg/L). PC945 (GM MIC=0.058 mg/L, 24 h reading) was 7.4-fold and 1.5-fold more potent than voriconazole and posaconazole, respectively, and the differences were statistically significant (Table 1 and Figure 1). For 48 h reading, PC945 (GM MIC=0.14 mg/L) was 6.7-fold and 1.9-fold more potent than voriconazole and posaconazole, respectively, and the differences were also statistically significant (Table 1 and Figure 1). Good correlation between PC945 and posaconazole/voriconazole MICs (Pearson $P<0.001$; Figure 2b and c) was observed, suggesting that any strain(s) having high MICs of PC945 also show high MICs of both posaconazole and voriconazole. At 48 h reading, two UK isolates that were less susceptible to PC945 were also less susceptible to both voriconazole and posaconazole. However, at 24 h reading, the same two UK isolates were susceptible to PC945, but not to posaconazole and voriconazole.

Sequencing of *ERG11* was performed for nine each of the UK and Indian isolates with high MICs of PC945. Of the Indian isolates, five showed a K143R mutation, two showed a Y132F mutation, one isolate had both K143R and Y132F mutations and one isolate did not show any known mutation in *ERG11*. All three UK isolates of the Pakistani/Indian clade showed a Y132F mutation and all six UK isolates of the South African clade showed an F126L mutation. *ERG11* mutation analysis of the CDC panel has been reported[16] and the data are included in Table 2. There was no correlation between mutation and PC945 MIC values.

Tentative ECOFFs were calculated using CLSI's ECOFF Finder. Those values were slightly different between different cut-off levels (95%, 97.5% and 99%, 99.9%) using MICs of either 24 h reading or 48 h reading (Table 3). At the 99% cut-off, the PC945 ECOFF was 4- to 16-fold lower than that of voriconazole.

Discussion

In the present study, we examined the *in vitro* susceptibility of *C. auris* isolates obtained from different parts of the world to PC945, a novel triazole optimized for inhaled or topical treatment, and PC945 was found to be a potent inhibitor of *C. auris* isolates, which are largely fluconazole resistant.

Our data showed that the MIC ranges of voriconazole (0.031 to >4 mg/L) and fluconazole (8 to >64 mg/L) for *C. auris* were similar to those previously reported,[17–20] suggesting that the results obtained in this study are comparable to those studies. There are no established MIC clinical breakpoints at present for *C. auris* drug susceptibility interpretation. The CDC recommends applying the conservative breakpoints developed for other *Candida* spp. to *C. auris* (32 mg/L for fluconazole, 2 mg/L for voriconazole) for epidemiological purposes. Arendrup *et al.*[20] described similar ECOFFs

Table 2. Susceptibility testing of the *C. auris* CDC panel and the CBS-KNAW panel to PC945 and other antifungal triazoles

Isolate	MIC (mg/L) of PC945[b]	MIC (mg/L) reported by CDC[a] (for CDC isolates)/Larkin *et al.*[32] (for CBS isolates)				Clade (for CDC isolates)/ isolated area (for CBS isolates)	*ERG11* mutation[16]
		FLC	VOR	POS	AMB		
CDC panel							
0381	0.016	4	0.03	0.06	0.38	East Asia	
0382	4	16	0.5	0.5	0.38	South Asia	
0383	2	128	4	0.5	0.38	Africa	F124L
0384	0.25	128	1	0.5	0.5	Africa	F124L
0385	0.25	>256	16	1	0.5	South America	Y132F
0386	0.25	>256	16	0.5	0.5	South America	Y132F
0387	0.25	8	0.6	0.25	0.75	South Asia	
0388	>4	>256	2	0.25	1.5	South Asia	K143R
0389	0.125	128	4	0.125	4	South Asia	Y132F
0390	0.25	>256	8	0.5	4	South Asia	K143R
GM MIC	0.41	97	1.9	0.33	0.81		
MIC_{50}	0.25	128	3.0	0.50	0.50		
MIC_{90}	4.4	>256	16	0.55	4.0		
CBS panel							
CBS10913	0.016	2				Japan (ear)	
CBS12372	1	>64				South Korea (blood)	
CBS12373	1	>64				South Korea (blood)	
GM MIC	0.25						
Quality control							
C. parapsilosis (ATCC 22019)	0.125						

AMB, amphotericin B; FLC, fluconazole; POS, posaconazole; VRC, voriconazole.
[a]Referred from https://www.cdc.gov/ARIsolateBank/Panel.
[b]Assays were conducted in accordance with CLSI M27 (third edition) and plates were read after 24 or 48 h of incubation (24 h read results are shown in Table S6).

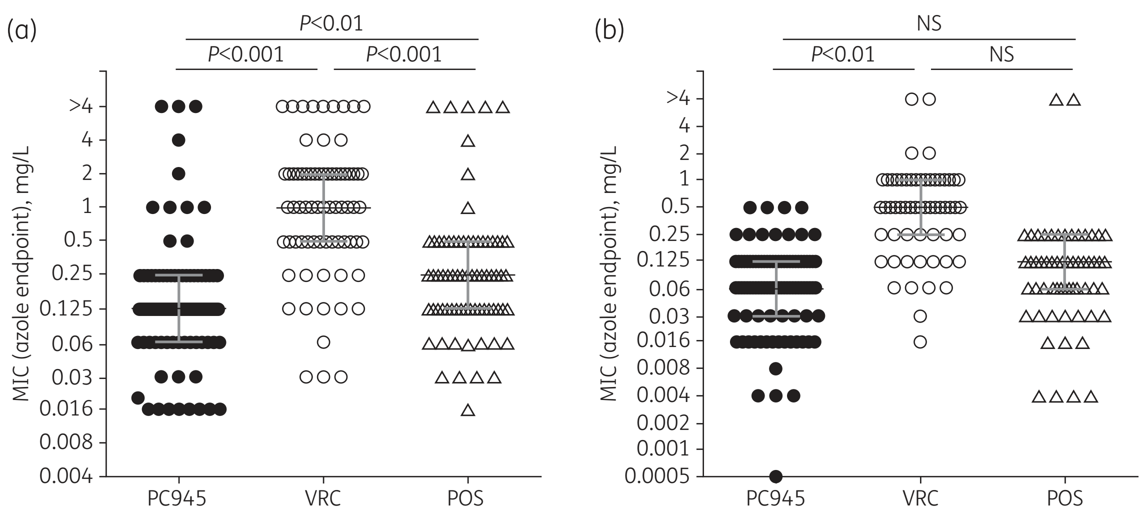

Figure 1. MIC distribution of PC945, voriconazole and posaconazole for all *C. auris* isolates tested. MICs of PC945, voriconazole and posaconazole determined by the CLSI method for all tested *C. auris* isolates are plotted. $P<0.01$ or 0.001 (Friedman test with Dunn's multiple comparison). NS, not significant; POS, posaconazole; VRC, voriconazole.

for itraconazole (ranges for CLSI/EUCAST=0.25–0.5/0.5–1 mg/L) and posaconazole (ranges for CLSI/EUCAST=0.125/0.125–0.25 mg/L), whereas for voriconazole the estimated ECOFFs varied widely (1–32 mg/L) and depended on the method applied. For the tested isolates, estimated ECOFFs calculated using CLSI's ECOFF Finder were 0.5–4 mg/L for posaconazole and 2–128 mg/L for voriconazole. According to ECOFF values (obtained in the present study and published), ∼17% or less of the Indian isolates were

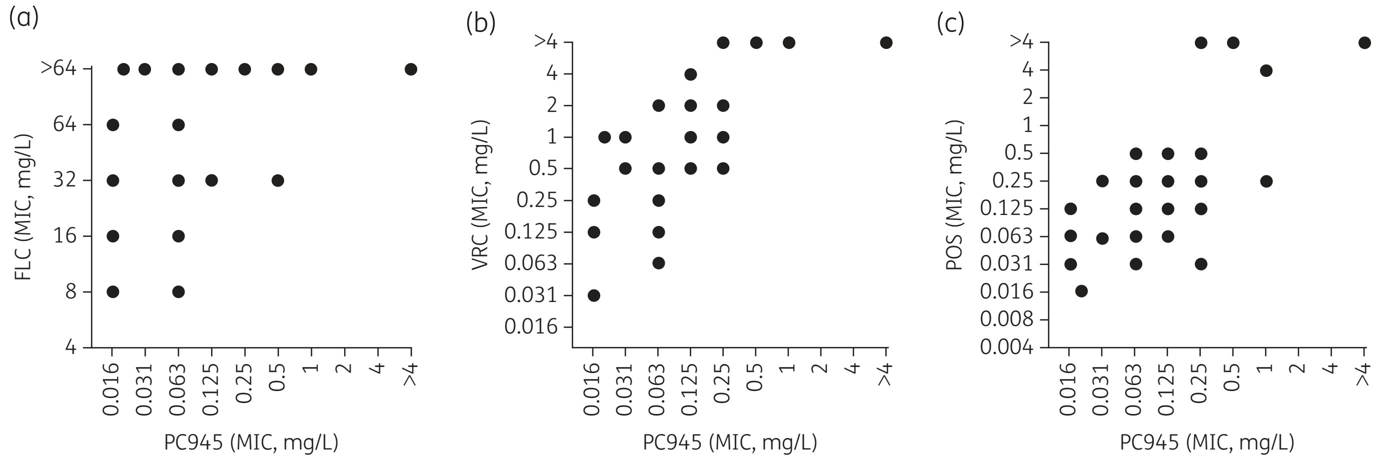

Figure 2. Individual MIC distribution and correlation. Relationship of MIC distribution for all *C. auris* between PC945 and fluconazole (a), voriconazole (b) or posaconazole (c) is shown. FLC, fluconazole; POS, posaconazole; VRC, voriconazole.

Table 3. Tentative ECOFFs for *C. auris* using four different endpoints

	24 h MIC					48 h MIC				
		tentative ECOFF[b]					tentative ECOFF[b]			
Compound	modal MIC (mg/L)	95%	97.5%	99%	99.9%	modal MIC (mg/L)	95%	97.5%	99%	99.9%
PC945	0.063	0.5	0.5	1	2	0.125	0.5	1	2	4
Fluconazole[a]	>64	NA	NA	NA	NA	>64	NA	NA	NA	NA
Voriconazole	0.5	2	4	4	16	2	16	16	32	128
Posaconazole	0.125	0.5	0.5	1	2	0.125	1	1	2	4

NA, not available (the ECOFF Finder program could not provide an ECOFF).
[a]Indian and UK strains only.
[b]ECOFF Finder (https://clsi.org/meetings/microbiology/ecoffinder/).

voriconazole resistant, 35% or less were posaconazole resistant and 75% were fluconazole resistant. The recent meta-analysis[3] showed that 44.29% of *C. auris* were resistant to fluconazole and 12.67% to voriconazole. Therefore, the present study suggests that Indian isolates are more resistant to fluconazole.

In all isolates tested in this study, PC945 (GM MIC=0.14 mg/L) was >457-, 6.8- and 1.9-fold more potent than fluconazole (>64 mg/L), voriconazole (0.95 mg/L) and posaconazole (0.26 mg/L), respectively, and the difference between PC945 and voriconazole/posaconazole was statistically significant (Figure 1). Only 3 out of 72 isolates tested [including 1 in the CDC panel (0388) and 2 UK isolates of the South African clade] were less susceptible to PC945.

Molecular analyses of the strains collected from different geographical regions have revealed that *C. auris* strains have emerged independently in multiple regions of the world.[21] Molecular typing of international strains (Eastern Asia, Southern Asia, Southern Africa and South America) performed by the CDC suggests that isolates are highly related within countries and regions but distinct between continents.[22] Cluster analysis showed that all species formed distinct clusters based on amplified fragment length polymorphism[23] (Indian strains were clustered separately from Japanese and South Korean strains). WGS has identified three different amino acid substitutions in the *ERG11* gene of *C. auris*.[23] These substitutions were strongly associated with geographical clades: F126T/F126L with South Africa, Y132F with Venezuela, and Y132F or K143F/K143R with India and Pakistan. Each mutation is associated with isolates from a different continent, implying that resistance to fluconazole might be acquired rather than intrinsic. We also confirmed that all South African clade UK isolates had F126L dominantly, Pakistani/Indian clade UK isolates had Y132F and Indian isolates had Y132F and/or K143R. However, we did not see any correlation between *ERG11* mutation and PC945 MIC. The direct role of efflux pumps in *C. auris* antifungal resistance is yet to be characterized but it has been indicated that *C. auris* expresses higher ABC-type efflux pump activity than *C. glabrata* and *Candida haemulonii*.[24] Thus, efflux pumps might play an important role in *C. auris* MDR mechanisms. In addition, resistance-conferring mutations in the *FKS* gene might be involved in the resistance mechanisms of *C. auris*.[15] The specific mechanism of voriconazole and posaconazole resistance remains unclear, but we observed good correlation between MICs of voriconazole/posaconazole and PC945 in an MIC distribution graph (Figure 2). This indicates that the isolates with low susceptibility to PC945 will have a similar resistance mechanism to that of voriconazole/posaconazole although further cross-resistance analysis is required. In fact, three isolates (including isolate 0388 in the CDC panel and two UK isolates) were less susceptible to posaconazole, voriconazole and PC945 although the molecular mechanism responsible for the increased MIC is still unclear.

Existing triazole compounds are usually dosed either orally or systemically and have several limitations such as unwanted systemic effects and poor or variable drug concentrations achieved at the site of infection.[25–27] *C. auris* has been isolated from upper and lower respiratory tract samples such as nasal swabs,[11] BALF,[8–10] sputum,[6] oral mucosa and pharyngeal secretions as well as from the air[11] in hospital settings. Hence, targeting upper or lower airway delivery by aerosolization of antifungals can prevent systemic side effects by achieving high local concentrations at the primary site of infection. In a murine model of invasive pulmonary aspergillosis, Tolman *et al.*[28] have demonstrated that prophylaxis with an aerosolized aqueous intravenous formulation of voriconazole significantly improved survival and limited the extent of invasive disease. Interestingly, mice that received aerosolized voriconazole had a survival advantage over controls and those treated with amphotericin B. Recently, the first case of successful use of inhaled PC945 to treat an *Aspergillus* bronchial anastomotic infection and tracheobronchitis in a lung transplant recipient refractory to systemic antifungal treatment has recently been published.[29] PC945 has been designed to be retained within the target organ (such as lung and nose) resulting in very low systemic exposure (data not shown) and reduction of the potential side effects. In addition, PC945 exhibits high levels of plasma protein binding, further reducing the likelihood of problems arising from circulating drug substance.

PC945 is the first antifungal triazole specifically designed as a once-daily, topical/aerosolized treatment for upper airway fungus colonization. PC945 is under clinical development.[30,31] Although the transmission route of *C. auris* has not been fully identified, these *in vitro* data of PC945 indicate that it is a promising drug to prevent or treat *C. auris* infection. However, further laboratory and clinical evaluations are warranted.

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Supplementary data

Tables S1 to S7 are available as Supplementary data at *JAC* Online.

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