In Vitro Activity of a Novel Cyp51 Inhibitor, VT-1598, Against Clinical Isolates of *Candida auris*

Sunday-304

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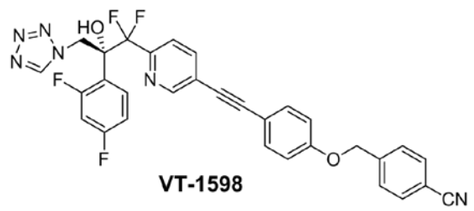
Introduction

- *Candida auris*, an emerging fungal pathogen that is associated with high mortality, has been identified in many countries across the world.
- It is often mistaken for other *Candida* species in the clinical laboratory and has shown a marked ability to withstand standard infection control practices. More troubling, *C. auris* can exhibit *in vitro* resistance to multiple antifungal agents, including the azoles, echinocandins, and/or amphotericin B – creating a challenge for clinicians directing treatment. (1-3)
- As the emergence of this serious threat to public health continues, it will be important to evaluate the efficacy of novel antifungal agents as potential avenues of therapy, as existing options may be inadequate.
- The aim of this study is to explore the *in vitro* susceptibility of a collection of 100 *C. auris* isolates against VT-1598, a novel fungal CYP51 inhibitor.
- These isolates represent each of the four known clades of *C. auris* and originate from diverse countries, including India, Pakistan, Colombia, South Africa, and the US. The collection includes isolates known to have elevated minimum inhibitory concentrations (MICs) against other CYP51 inhibitors including fluconazole. (3)

Methods

Testing was performed according to the standards of the Clinical and Laboratory Standards Institute reference methodology M27-A3. (4) The test compound was dissolved in DMSO and diluted as described in M27-A3 to give a final DMSO concentration of 1%. Dilution plates were stored at -70°C until used and were used within one week of being produced. All results were read visually after 24 hours of incubation at the lowest drug concentration at which there was a 50% decrease in growth by visual inspection. Quality control isolates *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were included on each day of testing although there are no standard QC values for these isolates against this compound. The MIC values for ATCC 22019 and ATCC 6258 remained within a tight range of 1-2 dilutions over the course of the study.

Compound Structure



VT-1598

(5)

Results

Table 1. MIC data for 100 *Candida auris* isolates

Compound	Minimum Inhibitory Concentration (µg/ml)
	VT-1598
Inhibition	50%
Range	0.03 - 8
Mode	0.25
MIC_{50}	0.25
MIC_{90}	1

Table 2. MIC data for fluconazole resistant vs. susceptible isolates

Fluconazole Interpretation	Minimum Inhibitory Concentration (µg/ml)	
	Susceptible	Resistant
No. Isolates	30	69
Range	0.03 - 8	0.03 - 8
Mode	0.25	0.25
MIC_{50}	0.125	0.25
MIC_{90}	0.25	1

- The overall mode and MIC_{50} were both 0.25 µg/mL, and the MIC_{90} was 1 µg/mL (Table 1).
- VT-1598 showed similar activity against all *C. auris* clades of in this collection and these MICs ranged from 0.03-8 µg/mL (Table 3).
- Eight isolates exhibited MICs higher than 1 µg/mL and were among a single clade.
- For fluconazole, the historical mode, MIC50, and MIC90 against this set was >256 µg/mL, 64 µg/mL, and >256 µg/ml.
- The VT-1598 MIC_{50} among fluconazole-susceptible isolates was similar to the value for fluconazole-resistant isolates (Table 2).
- Trailing growth was observed among a majority of isolates, which is often seen with fungal CYP51 inhibitors and *Candida* spp.

Table 3. Distribution of MIC values

MIC	<0.016	0.016	0.03	0.0625	.125	.25	.5	1	2	4	8	16	>16
No. of Isolates			2	4	26	33	19	8			8		

Conclusions

This project details the *in vitro* susceptibilities of a large collection of *C. auris* to the novel compound VT-1598. While there are no interpretive breakpoints for *C. auris* against VT-1598, these MIC values indicate widespread activity. The activity across the 4 clades are comparable, suggesting that any genetic diversity arising between geographically-distinct isolates does not influence the activity of the compound. Interestingly, the MIC_{50} value for this compound among fluconazole susceptible isolates was similar to the value for fluconazole resistant isolates, indicating that resistance to azole antifungals is not suggestive of resistance to this compound.

Contact Information

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References

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