The Novel Fungal Cyp51 Inhibitor VT-1598 Demonstrates Potent In Vitro Activity Against *Candida* and *Cryptococcus* Species

N.P. Wiederhold, B.H. Tran, H. Patterson, C.M. Yates, R.J. Schotzinger, E.P. Garvey
UT Health San Antonio, Viamet Pharmaceuticals, Ltd.

Contact Information:
N.P. Wiederhold
UTHSCSA
7703 Floyd Curl Dr., MC 7750
San Antonio, TX 78229
Tel: (210) 567-4086
e-mail: wiederholdn@uthscsa.edu

ABSTRACT

Background: Available antifungals are limited by toxicities, drug interactions, or lack of oral formulations. VT-1598 is a novel tetrazole-based inhibitor of fungal Cyp51 that is being developed for oral administration. We evaluated the in vitro activity of VT-1598 against a collection of clinical isolates of *Candida* and *Cryptococcus* species, including those resistant to available drugs.
Methods: 123 clinical *Candida* (72 *C. albicans,* 32 *C. glabrata,* 10 *C. parapsilosis,* & 9 *C. tropicalis*) and 52 *Cryptococcus* isolates (36 *C. neoformans* & 16 *C gattii*) were used. Minimum inhibitory concentrations (MICs) were measured by broth dilution using CLSI M27-A3 methods. Positive controls included fluconazole (FLC) and caspofungin (CAS) against *Candida*, and FLC and amphotericin B (AMB) against *Cryptococcus*. Differences in geometric mean (GM) MIC values were assessed for significance by ANOVA.
Results: VT-1598 demonstrated potent in vitro activity against *Candida*. VT-1598 MICs against all *C. albicans* isolates tested were ≤0.002->1 μg/ml, and geometric mean (GM) MIC values were lower than those for FLC and CAS. Against *C. glabrata, C. parapsilosis,* and *C. tropicalis*, VT-1598 MICs ranged between ≤0.015-1 μg/ml, with GM MIC values also lower than those observed for FLC and CAS. VT-1598 also maintained potent activity against some *C. albicans* and *C. glabrata* isolates that were resistant to FLC (VT-1598 MIC 0.008->1 μg/ml & 0.03->8 μg/ml, respectively). Potent activity was also observed against *Cryptococcus*. VT-1598 MICs against *C. neoformans* and *C. gattii* ranged between 0.004-0.25 μg/ml and ≤0.025-0.25 μg/ml, respectively. VT-1598 GM MICs against these species were also lower than those for FLC and AMB.
Conclusions: VT-1598 demonstrated potent in vitro activity against clinical isolates of *Candida* and *Cryptococcus*. This investigational fungal Cyp51 inhibitor also maintained potent activity against many FLC-resistant isolates. These in vitro data suggest that clinical investigation of this promising novel agent is warranted.

BACKGROUND & OBJECTIVE

- *Candida* species are currently the fourth most common cause of nosocomial bloodstream infections in the United States, with the most prevalent species being *C. albicans, C. glabrata, C. parapsilosis,* and *C. tropicalis*.
- Cryptococcosis caused by *Cryptococcus neofrmans* is a significant cause of morbidity and mortality world-wide in HIV/AIDS patients. Infections caused by *C. gattii* can also occur in immunocompetent patients.
- Current treatment strategies for invasive infections caused by these pathogens include the use of the azoles, amphotericin B, or the echinocandins. Although effective, each of these classes has drawbacks that may limit clinical responses. These may include toxicities, drug interactions, and the development of resistance.
- VT-1598 is a novel tetrazole-based antifungal that is specific for fungal Cyp51 and is currently being developed for oral treatment of chronic invasive fungal infections
- Our objective was to evaluate the in vitro activity of VT-1598 against a collection of clinical isolates of *Candida* and *Cryptococcus* species, including those resistant to clinically available agents.

METHODS

- 123 clinical *Candida* (72 *C. albicans,* 32 *C. glabrata,* 10 *C. parapsilosis,* & 9 *C. tropicalis*) and 52 *Cryptococcus* isolates (36 *C. neoformans* & 16 *C gattii*) were used.
- Minimum inhibitory concentrations (MICs) were measured by broth dilution using CLSI M27-A3 methods.
- MICs for VT-1598, fluconazole, and caspofungin were read after 24 hours and 72 hours for *Candida* and *Cryptococcus* species, respectively, as the lowest concentration that resulted in 50% inhibition of growth. For amphotericin B MICs were read at 100% inhibition of growth.
- MIC values were transformed to $\log_2$ scale, and differences in geometric mean (GM) MIC values were assessed for significance by t-test and ANOVA.

RESULTS

Figure 1A, B, C & D, and Tables 1 & 2. In vitro activity of VT-1598, Fluconazole, and Caspofungin against Clinical Isolates of *Candida* Species; *p-value < 0.05 vs. VT-1598.

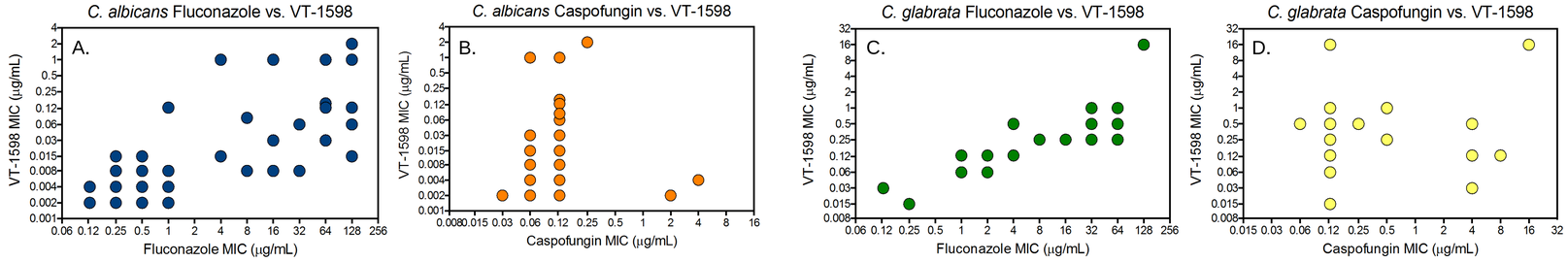


Table 1	*C. albicans* Fluconazole Susceptible (n=48)			*C. albicans* Fluconazole Resistant (n = 21)		
Antifungal	VT-1598	Fluconazole	Caspofungin	VT-1598	Fluconazole	Caspofungin
MIC range	≤0.002-0.12	0.125-1	0.03-4	0.008->1	8->64	0.06-0.25
MIC50	0.004	0.25	0.06	0.06	64	0.12
MIC90	0.008	1	0.125	>1	>64	0.12
GM MIC	0.004	0.277*	0.083*	0.124	49.1*	0.112

Table 2	*C. glabrata* Fluconazole SDD (n = 24)			*C. glabrata* Fluconazole Resistant (8)		
Antifungal	VT-1598	Fluconazole	Caspofungin	VT-1598	Fluconazole	Caspofungin
MIC range	≤0.015-1	≤0.12-32	0.12->8	0.25->8	64->64	0.06->8
MIC50	0.12	2	0.12	0.5	64	0.125
MIC90	1	32	4	16	>64	4
GM MIC	0.147	3.00*	0.236	1.19	76.1*	0.35

Figure 2A, B, C & D, and Tables 3 & 4. In vitro activity of VT-1598, Fluconazole, and Caspofungin against Clinical Isolates of *Candida* Species; *p-value < 0.05 vs. VT-1598.

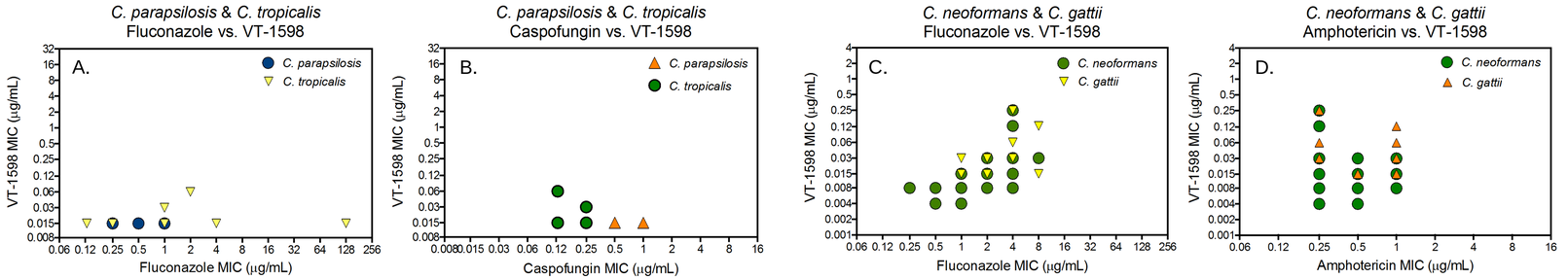
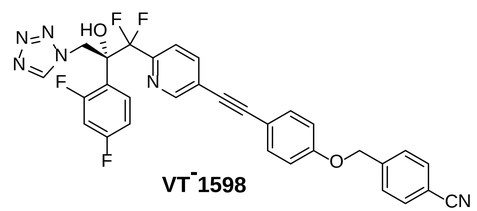


Table 3	*C. parapsilosis* (n = 10)			*C. tropicalis* (n = 9)		
Antifungal	VT-1598	Fluconazole	Caspofungin	VT-1598	Fluconazole	Caspofungin
MIC range	≤0.015	0.25-1	0.5-1	≤0.015-0.06	0.12->64	0.12-0.25
MIC50	≤0.015	0.5	1	≤0.015	1	0.12
MIC90	≤0.015	0.5	1	0.03	>64	0.25
GM MIC	≤0.015	0.406*	0.758*	0.019	2.00*	0.146*

Table 4	*C. neoformans* (n = 36)			*C. gattii* (n = 16)		
Antifungal	VT-1598	Fluconazole	Amphotericin	VT-1598	Fluconazole	Amphotericin
MIC range	0.004-0.25	0..25-8	0.25-1	≤0.015-0.25	1-8	0.25-1
MIC50	0.015	2	0.5	0.03	2	1
MIC90	0.03	4	1	0.12	8	1
GM MIC	0.016	1.89*	0.463*	0.039	2.71*	0.738*



CONCLUSIONS

VT-1598 demonstrated potent in vitro activity against clinical isolates of *Candida* and *Cryptococcus* species. These included isolates of *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* as well as *C. neoformans* and *C. gattii*. This investigational, fungal-specific Cyp51 inhibitor also maintained potent activity against many fluconazole-resistant isolates. These in vitro data suggest that clinical investigation of this promising novel agent is warranted.

Support and VT-1598 powder provided by Viamet Pharmaceuticals, Inc., Durham, N.C..