The Novel Fungal Cyp51 Inhibitor VT-1598 Demonstrates Potent In Vitro Activity Against Endemic Fungi, *Aspergillus*, and *Rhizopus*

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: Treatment options for invasive mycoses due to opportunistic endemic fungi and moulds may be limited by toxicities and drug interactions of available drugs. VT-1598 inhibits ergosterol biosynthesis through specific inhibition of fungal Cyp51. Our objective was to evaluate the in vitro activity of VT-1598 against a collection of clinical isolates of endemic fungi, *Aspergillus* spp., and *Rhizopus arrhizus*.

Methods: 40 clinical isolates of *Coccidioides* sp., 12 of *B. dermatitidis,* 13 of *H. capsulatum*, 84 of *Aspergillus,* and 11 of *R. arrhizus,* were used. Minimum inhibitory concentrations (MICs) were measured by broth dilution according to CLSI M38-A2 methods. Positive controls included posaconazole (PSC), voriconazole (VRC), amphotericin B (AMB), and fluconazole (FLC). Differences in geometric mean (GM) MIC values were assessed for significance by ANOVA.

Results: VT-1598 demonstrated potent in vitro activity against endemic fungi, with MICs of 0.06-0.5 μg/ml for *Coccidioides* spp., and ≤0.03-0.5 μg/ml for both *B. dermatitidis* and *H. capsulatum.* VT-1598 GM MICs were similar to that of PSC and lower than that of FLC against these endemic species. Potent in vitro activity was also observed for VT-1598 against *Aspergillus* and *R. arrhizus*. MICs ranged between 0.25->16 μg/ml for *A. fumigatus*, 0.25-0.1 μg/ml for *A. flavus*, 0.25-1 μg/ml for *A. terreus,* and 1->16 μg/ml for *A. niger*. Geometric mean (GM) MIC values were similar to those of PSC and VRC against *Aspergillus*. Against *R. arrhizus*, VT-1598 ranged from 0.5->16 μg/ml (0.25-16 μg/ml for *R. arrhizus* var. *arrhizus,* 1->16 μg/ml for *R. arrhizus* var. *delemar*) compared to 1-2 μg/ml for PSC and 0.25-1 μg/ml for AMB.

Conclusions: VT-1598 demonstrated potent in vitro activity against various endemic fungi and moulds. These included species that are major causes of coccidioidomycosis (aka, Valley Fever) and other endemic infections, invasive aspergillosis, and mucormycosis. These data warrant further investigation of this novel broad-based and selective fungal CYP51 inhibitor.

BACKGROUND & OBJECTIVE

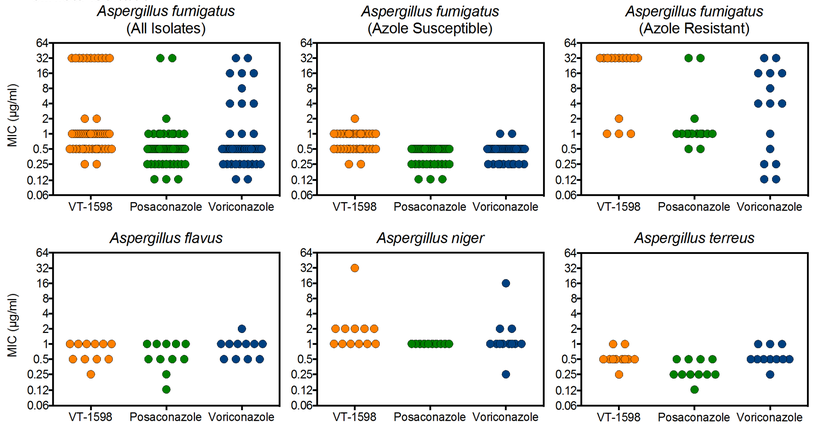
- Endemic fungal infections caused by the dimophic fungi *Coccidioides* spp., *Blastomyces dermatitidis*, and *Histoplasma capsulatum*, can occur in immunocompromised and immunocompetent individuals.
- Invasive fungal infections caused by opportunistic moulds, such as *Aspergillus* spp. (including *A. fumigatus, A. flavus, A. niger,* and *A. terreus*), and *Rhizopus arrhizus*, are significant causes of morbidity and mortality in immunocompromised hosts.
- Current treatment strategies for invasive infections caused by these pathogens include the use of the azoles and amphotericin B,. 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 endemic fungi, as well as opportunistic and moulds, including those resistant to clinically available azoles.

METHODS

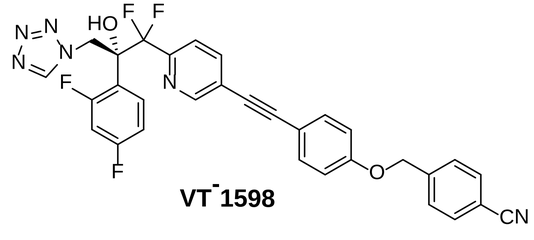
- 160 clinical fungal isolates (40 *Coccidioides* spp., 12 *B. dermatitidis,* 13 *H. capsulatum,* 84 *Aspergillus* spp. and 11 *R. arrhizus*) were used.
- Minimum inhibitory concentrations (MICs) were measured by broth dilution using CLSI M38-A2 methods.
- MICs were read between 24 – 48 hours as the lowest concentration that resulted in 100% inhibition of growth against *Aspergillus* and *R. arrhizus*. Against endemic fungi, MICs were read between 48 – 168 hours as the lowest concentration that resulted in 80% 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 1 & Table 1. In vitro activity of VT-1598, Posaconazole, & Voriconazole against *Aspergillus* clinical isolates.

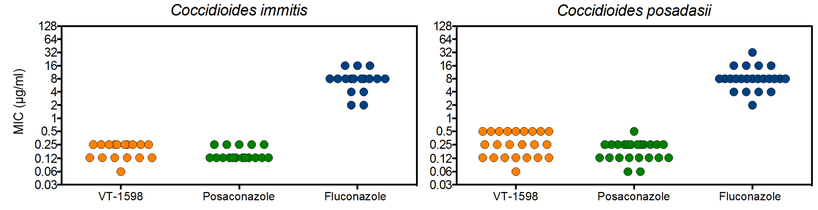


Group	*A. fumigatus* (all isolates n = 50)			*A. fumigatus* (azole susceptible = 45)		
Antifungal	VT-1598	Posaconazole	Voriconazole	VT-1598	Posaconazole	Voriconazole
MIC range	0.15 - >16	0.12->16	0.12->16	0.25-2	0.12-0.5	0.25-1
MIC50	1	0.5	0.5	0.5	0.5	0.5
MIC90	>16	1	8	1	0.5	0.5
GM MIC	1.67	0.551	0.727	0.686	0.357	0.427
Group	*A. fumigatus* (azole resistant n = 15)			*A. flavus* (n = 11)		
Antifungal	VT-1598	Posaconazole	Voriconazole	VT-1598	Posaconazole	Voriconazole
MIC range	1->16	0.5->16	0.12->16	0.25-1	0.12-1	0.5-2
MIC50	>16	1	4	1	0.5	1
MIC90	>16	>16	>16	1	1	1
GM MIC	13.3	1.52	2.52	0.685	0.567	0.828
Group	*A. niger* (n = 12)			*A. terreus* (n = 11)		
Antifungal	VT-1598	Posaconazole	Voriconazole	VT-1598	Posaconazole	Voriconazole
MIC range	1->16	1	0.25-16	0.25-1	0.12-0.5	0.25-1
MIC50	1	1	1	0.5	0.25	0.5
MIC90	2	1	2	1	0.5	1
GM MIC	1.78	1.00	1.26	0.533	0.302	0.567



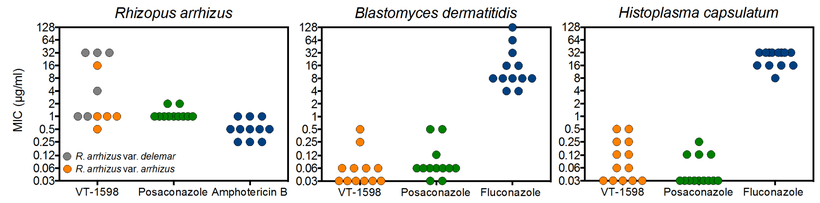
VT-1598

Figure 2 & Table 2. In vitro activity of VT-1598, Posaconazole, & Fluconazole against *C. immitis* & *C. posadasii*.



Species	*Coccidioides immitis* (n = 17)			*Coccidioides posadasii* (n = 23)		
Antifungal	VT-1598	Posaconazole	Fluconazole	VT-1598	Posaconazole	Fluconazole
MIC range	0.06-0.25	0.12-0.25	2-16	0.06-0.5	0.06-0.5	2-32
MIC50	0.25	0.12	8	0.25	0.25	8
MIC90	0.25	0.25	16	0.5	0.25	16
GM MIC	0.180	0.153	7.08	0.250	0.179	8.00

Figure 3 & Table 3. In vitro activity of VT-1598, Posaconazole, & Amphotericin against *R. arrhizus* clinical isolates, and VT-1598, Posaconazole, & Fluconazole against *B. dermatitidis* & *H. capsulatum*.



Species	*Rhizopus arrhizus* (n = 17)			*Blastomyces dermatitidis* (n = 23)		
Antifungal	VT-1598	Posaconazole	Amphotericin	VT-1598	Posaconazole	Fluconazole
MIC range	0.5->16	1-2	0.25-1	≤0.03-0.5	≤0.03-0.5	4->64
MIC50	1	1	0.5	≤0.03	0.06	8
MIC90	>16	2	1	0.25	0.5	64
GM MIC	3.53	1.13	0.500	0.057	0.081	13.5

Species	*Histoplasma capsulatum* (n = 17)		
Antifungal	VT-1598	Posaconazole	Fluconazole
MIC range	≤0.03-0.5	≤0.03-0.25	8-32
MIC50	0.06	0.03	32
MIC90	0.5	0.12	32
GM MIC	0.089	0.049	23.2

CONCLUSIONS

VT-1598 demonstrated potent in vitro activity against various endemic fungi and moulds. This included species that are major causes of coccidioidomycosis (aka, Valley Fever) and other endemic infections, invasive aspergillosis, as well as mucormycosis. These data warrant further investigation of this novel broad-based and selective fungal CYP51 inhibitor.

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