In Vitro Activity of Two Metalloenzyme Inhibitors Compared to Caspofungin and Fluconazole Against a Panel of 74 *Candida* spp.

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Abstract

Despite advances in antifungal therapy, patients with fungal infections continue to fail therapy with currently available antifungal agents. As a result, the need for new antifungal agents is imperative. Two investigational compounds, VT-1129 and VT-1161 provided by Viamet Pharmaceuticals (Morrisville, NC) have been evaluated for antifungal activity. These compounds are novel metalloenzyme inhibitors and showed excellent activity against *Candida* species tested. Activity was compared to the commercially available drugs, caspofungin (CAS) and fluconazole (FLC). Isolates tested included *Candida albicans* (10), *C. albicans* – azole resistant (10), *C. albicans* – candin resistant (5), *C. glabrata* (10), *C. glabrata* – azole resistant (10), *C. glabrata* -– candin resistant (5), *C. parapsilosis* (10), *C. guilliermondii* (3), *C. krusei* (3), *C. lusitaniae* (3), *C. tropicalis* (5) In addition, CLSI QC strains (*C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258) were included. With the exception of the controls, all isolates were clinical samples submitted to the Fungus Testing Laboratory for susceptibility testing and/or identification.

Material and Methods

Methods for testing were those outlined in the CLSI document M27-A2. All drugs were tested in a microdilution format using RPMI-1640, incubated at 35˚C, and read manually with an inverted mirror. Testing range for VT compounds was 0.03-16 µg/ml while the range for CAS was 0.015-8 µg/ml and for FLC was 0.125-64 µg/ml. Not knowing the correct endpoint percent inhibition for these compounds, endpoints were determined at both 50% and 100% inhibition of fungal growth as compared to the drug-free growth control. Endpoints for CAS and FLU were determined at the lowest concentration that resulted in 50% inhibition of growth.

A 10 mg portion of VT powders was weighed out and added to 1 ml of DMSO for a stock concentration of 10,000 µg/ml. Further dilutions were made in DMSO and subsequently diluted in RPMI for a final DMSO concentration of 1%.

Results

	Agent	VT-1129 (50/100%)		VT-1161 (50/100%)		CAS	FLC
	Time	24 hrs	48 hrs	24 hrs	48 hrs	24 hrs	24 hrs
CA N=25	MIC50	≤0.03/>16	≤0.03/>16	≤0.03/>16	≤0.03/>16	0.06	≤0.125
	MIC90	≤0.03/>16	≤0.03/>16	≤0.03/>16	≤0.03/>16	0.125	0.25
	Range	≤0.03->16	≤0.03->16	≤0.03->16	≤0.03->16	0.03-0.125	≤0.125-0.25
CA-FR N-10	MIC50	0.5/>16	2/>16	1/>16	1/>16	0.5	>64
	MIC90	>16	>16	>16	>16	1	>64
	Range	0.25->16	0.25->16	0.25->16	0.25->16	0.25-1	>64
CA-CR N-5	Range	≤0.03->16	≤0.03->16	≤0.03->16	≤0.03->16	4-8	≤0.125->64
CG N=25	MIC50	≤0.03/0.5	0.25/>16	0.06/0.5	0.25/>16	0.5	1
	MIC90	0.25/2	1/>16	0.25/2	1/>16	0.5	8
	Range	≤0.03-4	0.06->16	≤0.03-2	0.125->16	0.5	0.5-64
CG-FR N-10	MIC50	1/1	4/>16	2/8	4/>16	0.5	>64
	MIC90	2/2	4/>16	2/>16	8/>16	0.5	>64
	Range	0.06->16	0.25->16	0.125->16	0.125->16	0.25-0.5	4->64
CG-CR N-5	Range	≤0.03->16	≤0.03->16	≤0.03->16	≤0.03->16	0.25->8	<0.125-8

Results

1. Both VT compounds had excellent activity against *C. albicans* and *C. glabrata* including some strains with reduced susceptibility to CAS and FLC.
2. Very good activity was noted with both VT compounds against *Candida parapsilosis* with a MIC_{50} of <0.03 at both reading points and a MIC_{90} of<0.03/0.125 (50/100%). These MICs were lower than those found for CAS (1/1) and FLC (0.25/0.25) for the $MIC_{50/90}$.
3. Activity against other less-frequently encountered *Candida* species including *C. guilliermondii, C. krusei, C. lusitaniae,* and *C. tropicalis* was similar to the findings for *Candida glabrata.*

Conclusions

The activity of VT compounds against *Candida* spp. compared favorably with both caspofungin and fluconazole. Based on compound activity, it is likely that the correct reading point is a 50% reduction in turbidity. The MIC values did not differ greatly between 24 and 48 hour readings but a considerable difference was noted when determining an endpoint at 100% versus 50% consistent with other known CYP51 approved drugs.

These compounds show very promising results and may be candidates for further development in an effort to improve the treatment of patients with fungal infections.

References

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