Activity of orotomide F901318 against clinical isolates of *Scedosporium* spp. and *Lomentospora prolificans*

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INTRODUCTION

Scedosporium/Lomentospora species are emerging pathogens with high mortality rates. They show low susceptibilities to several antifungal agents, being all of them considered multiresistant. Therefore, new antifungal drugs that act via novel mechanisms are needed in order to overcome this ever-growing problem of resistance to current therapies.

The orotomides are a new chemical class of drugs whose most representative antifungal is F901318. This synthetic small molecule inhibits DHODH (dihydroorotate dehydrogenase), which is a key enzyme involved in pyrimidine synthesis (Oliver et al., 2016), and has shown good activity against several mold species including azole resistant *Aspergillus* (Buil et al., 2017).

The aim of this study was to evaluate the activity of F901318 and other antifungals against a collection of clinical isolates of *Scedosporium/Lomentospora*.

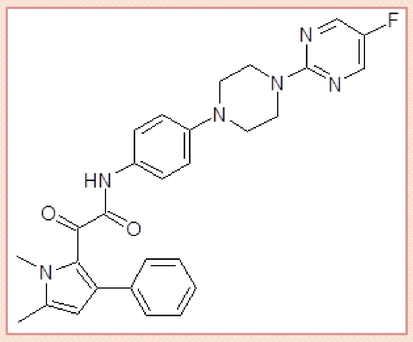


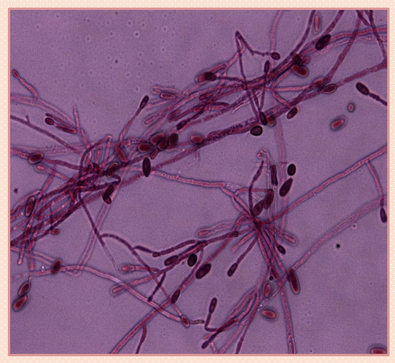
Figure 1. Structure of F901318 molecule (MW = 499; Formula = $C_{28}H_{27}FN_6O_2$).

MATERIALS AND METHODS

123 strains were tested for antifungal susceptibility following EUCAST 9.2 and CLSI M38A methodologies. All strains were isolated from clinical samples and identified to species level by sequencing the Internal Transcribed Spacer Region (ITS) of the rDNA and part of the beta tubulin gene (exons 5 and 6).

The antifungals included were amphotericin B (range 0.03-16 mg/L), isavuconazole (0.015-8 mg/L), voriconazole (0.015-8mg/L), micafungin (0.004-2 mg/L) and F901318 (0.004-2 mg/L). *A. flavus* ATCC204304 and *A. fumigatus* ATCC204305 were used as quality control strains.

Minimal Inhibitory Concentrations (MICs) for amphotericin B, Isavuconazole, voriconazole and F901318 and Minimum Effective Concentration (MECs) for micafungin were read after 24, 48 and 72 hours of incubation.



RESULTS

CLSI and EUCAST values were comparable at the defined incubation times (48 hours for EUCAST and 72 hours for CLSI). In general, CLSI showed lower MICs than EUCAST at 72 hours for amphotericin B and micafungin while isavuconazole, voriconazole and F901318 MICs were lower for EUCAST than for CLSI. At 24 hours, some strains showed no growth in both methods (21-31% in EUCAST and 41-48% in CLSI). All species showed MIC_{50} > 2 mg/L for amphotericin B and isavuconazole. Voriconazole had MIC_{50} and MIC_{90} ≤ 2 mg/L for all species except for *L. prolificans*. Micafungin showed MIC_{50} ≤ 0.5 mg/L against S. *apiospermum, S. boydii, S. ellipsoideum* and *S. dehoogii*, but MIC_{50} = 4 mg/L for *S. aurantiacum* and *L. prolificans*. F901318 was the only compound with low MICs against all species and strains tested, including the multiresistant species *Lomentospora prolificans* (MIC_{50} = 0.25 mg/L; MIC_{90}/MIC_{100} = 1 mg/L) (Table 1).

		EUCAST (48H)					CLSI (72H)				
		AMB	ISAV	VCZ	MCF	F901318	AMB	ISAV	VCZ	MCF	F901318
***S. apiospermum* (30)**	GM MIC/MEC	4.000	8.187	0.933	0.166	0.050	2.764	10.079	1.414	0.133	0.173
	MIC_{50}/MEC_{50}	4	8	1	0.25	0.06	2	16	1	0.12	0.25
	MIC_{90}/MEC_{90}	16	16	2	0.25	0.12	16	16	2	0.25	0.25
	Range MIC/MEC	0.5-32	2-16	0.5-2	0.015-0.5	0.015-0.12	0.25-16	1-16	0.5-8	0.03-1	0.03-0.5
***S. boydii* (30)**	GM MIC/MEC	12.126	6.063	0.706	0.214	0.040	6.650	7.639	0.977	0.136	0.127
	MIC_{50}/MEC_{50}	16	8	0.5	0.25	0.03	8	8	1	0.12	0.12
	MIC_{90}/MEC_{90}	32	16	2	0.5	0.12	32	16	2	0.5	0.25
	Range MIC/MEC	0.5-32	0.5-16	0.12-16	0.06-4	0.007-0.25	0.5-32	1-16	0.5-2	0.03-0.5	0.06-0.5
***S. ellipsoideum* (10)**	GM MIC/MEC	19.698	8.000	1.000	0.130	0.052	14.929	16.000	1.320	0.150	0.186
	MIC_{50}/MEC_{50}	16	8	1	0.12	0.06	16	16	1	0.12	0.25
	MIC_{90}/MEC_{90}	32	16	2	0.25	0.12	32	16	2	0.25	0.5
	Range MIC/MEC	8-32	2-16	0.5-2	0.06-0.25	0.015-0.5	2-32	16-16	1-2	0.12-0.25	0.06-1
***S. dehoogii* (3)**	GM MIC/MEC	32.000	10.079	0.794	0.250	0.095	20.159	8.000	1.000	0.250	0.250
	Range MIC/MEC	32-32	4-16	0.5-1	0.25-0.25	0.06-0.12	16-32	8-8	1-1	0.25-0.25	0.25-0.25
***S. aurantiacum* (20)**	GM MIC/MEC	22.627	9.514	0.966	3.249	0.130	7.210	14.420	1.366	3.357	0.339
	MIC_{50}/MEC_{50}	32	8	1	4	0.12	8	16	2	4	0.5
	MIC_{90}/MEC_{90}	32	16	2	4	0.25	16	16	2	4	1
	Range MIC/MEC	8-32	4-16	0.5-4	0.25-4	0.03-0.25	2-32	8-16	0.5-2	0.12-4	0.06-1
***L. prolificans* (30)**	GM MIC/MEC	24.818	15.635	12.699	3.732	0.115	17.959	15.635	16.000	3.732	0.225
	MIC_{50}/MEC_{50}	32	16	16	4	0.12	32	16	16	4	0.25
	MIC_{90}/MEC_{90}	32	16	16	4	0.25	32	16	16	4	0.5
	Range MIC/MEC	2-32	8-16	4-16	0.5-4	0.03-0.25	2-32	8-16	16-16	0.5-4	0.06-0.5

Table 1. Geometric mean (GM), MIC_{50}/MEC_{50} , MIC_{90}/MEC_{90} and range per species at 48 hours of incubation by EUCAST and 72 hours of incubation by CLSI for all drugs tested. MIC/MEC_{50} and MIC/MEC_{90} were only calculated when more than five strains were tested.

CONCLUSIONS

1. All *Scedosporium* species tested show high MICs to amphotericin B and isavuconazole;
2. Voriconazole was active against all species but *Lomentospora prolificans*;
3. Micafungin was active against all species but *S. aurantiacum* and *L. prolificans*;
4. F901318 was the only active compound against all species and strains tested with $MICs_{100}$ < 2 mg/L.

REFERENCES

- Buil *et al.*, 2017. In vitro activity of the novel antifungal compound F901318 against difficult-to-treat *Aspergillus* isolates. Journal of Antimicrobial Chemotherapy. 72 (9): 2548-2552.
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