The in vitro susceptibilities to the novel triazole isavuconazole and six other antifungal agents of a large collection of Rasamsonia isolates (n = 47) belonging to seven species were determined. Isavuconazole and voriconazole had no in vitro activity (MIC, >32 mg/liter) against isolates of the Rasamsonia argillacea species complex. The echinocandins were the most potent antifungal drugs against all of the isolates tested (minimum effective concentration, ≤0.19 mg/liter).

On the basis of phenotypic, physiological, and molecular data, the genus Rasamsonia was introduced to accommodate thermotolerant and thermophilic Penicillium-like species that produce cylindrical phialides that usually gradually taper toward the apices, distinctly rough-walled stipes and metulae, olive-brown conidia, and ascomata, if present, with a scanty covering (1). In 2013, the Rasamsonia argillacea species complex was investigated and currently consists of four species: R. argillacea sensu lato, R. eburnea, R. piperina, and R. aegroticola (2). R. cylindrospora and R. brevistipitata were shown to be phenotypically similar but genetically more distant (1).

Rasamsonia can be isolated from hot environments and clinical samples, and species belonging to the R. argillacea complex were described as an emerging fungus in immunocompromised hosts and cystic fibrosis patients (3). In particular, this pathogen was reported to cause invasive, disseminated infections in patients with chronic granulomatous diseases or hematological malignancies (4–7).

Isavuconazole, a novel triazole with broad-spectrum antifungal activity, showed noninferiority to voriconazole for the primary treatment of suspected invasive mold disease (8). In addition, isavuconazole showed activity against mucormycosis with efficacy similar to that of amphotericin B (9) and demonstrated clinical activity against Cryptococcus spp. and dimorphic fungi (10).

The objective of this study was to analyze the in vitro activity of isavuconazole and other antifungal agents against isolates from the R. argillacea species complex and those closely related to them. A collection of 47 clinical and reference isolates were included in the study. A detailed description of 35 isolates and the method used for identification was published previously (11). The additional 12 isolates were patient isolates from the University Hospital Essen, Essen, Germany.

Susceptibility testing was performed with EUCAST E.Def 9.3 as recently described (12). All of the isolates were cultured on malt agar (Oxoid, Wesel, Germany) before testing. The drug concentrations used ranged from 0.0625 to 32 mg/liter for isavuconazole, (Basilea, Basel Switzerland), voriconazole (Sigma-Aldrich, Munich, Germany), and amphotericin B (Sigma-Aldrich); from 0.03125 to 16 mg/liter for posaconazole (Hycurcet, Beutelsbach, Germany) and itraconazole (Sigma-Aldrich); and from 0.0078 to 4 mg/liter for micafungin (Hycurcet) and caspofungin (Sigma-Aldrich). A stock isavuconazole solution (Basilea, Basel Switzerland) was dissolved in dimethyl sulfoxide (Sigma-Aldrich) in accordance with the manufacturer’s instructions. After inoculation, the prepared plates were incubated at 36°C for 2 days and visually assessed. The minimum effective concentrations (MECs) of miconafungin and caspofungin were determined microscopically as the lowest concentrations of the drugs promoting abnormal, short, and branched hyphal clusters (12). For calculation of the geometric mean (GM), MICs of >16 mg/liter were set at 32 mg/liter. A clinical Aspergillus fumigatus isolate and a Candida parapsilosis reference strain (ATCC 22019) recommended by EUCAST were used as controls. Isavuconazole breakpoints are defined for A. fumigatus (≤1 mg/liter for susceptible, >1 mg/liter for resistant) by EUCAST version 8.0 (valid from 16 November 2015).

The in vitro susceptibilities (the GM and range of the MIC) of the different Rasamsonia isolates to isavuconazole and the other antifungals are shown in Table 1. The isavuconazole MICs for all of the isolates in the R. argillacea species complex (R. argillacea, R. aegroticola, R. eburnea, and R. piperina) were high (>32 mg/liter). Voriconazole had also no activity against isolates in the R. argillacea species complex. The GMs of the MICs of amphotericin B, posaconazole, and itraconazole were variable. The MECs of miconafungin and caspofungin for all of the Rasamsonia isolates were low. For R. cylindrospora and R. brevistipitata, the overall MICs/MECs of all of the antifungals tested were low.

Here, we show for the first time that the isavuconazole MICs for the emerging pathogenic R. argillacea species complex in vitro are high, suggesting no meaningful activity.

It was shown that isavuconazole has potent in vitro activity against most common Aspergillus species, P. lilacinum (= Paecilomyces lilacinus), and Scedosporium apiospermum (13, 14). The MICs for fungi of the family Mucoraceae varied between the genera (15).

The finding that the MICs of voriconazole were high and the MECs of echinocandins were low for R. aegillacea is consistent with a previous report in which susceptibility testing was performed by the broth microdilution method of the CLSI (M38-A2) (2). R. cylindrospora and R. brevistipitata, both exhibiting low isavuconazole MICs, were mostly isolated from the environment...
TABLE 1 *In vitro* susceptibilities of *Rasamsonia* species to seven antifungal agents, including isavuconazole

<table>
<thead>
<tr>
<th>Species (no. of isolates tested)</th>
<th>Value</th>
<th>MIC (mg/liter)</th>
<th>MEC (mg/liter)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Isavuconazole</td>
<td>Itraconazole</td>
</tr>
<tr>
<td><em>R. argillacea</em> (28)</td>
<td>For 50% of isolates &gt;32 &gt;16 &gt;32 4 1 0.125 0.03</td>
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<tr>
<td></td>
<td>For 90% of isolates &gt;32 &gt;16 &gt;32 &gt;16 8 0.25 0.125</td>
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<tr>
<td></td>
<td>Range &gt;32 1 to &gt;16 &gt;32 1 to &gt;16 0.5–32 0.125–0.25 0.015–0.25</td>
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<tr>
<td><em>R. aerotricola</em> (3)</td>
<td>Range &gt;32 2 to &gt;16 &gt;32 1–4 1–8 0.125–0.25 0.03–0.125 0.06–0.25 0.015–0.06</td>
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</tr>
<tr>
<td><em>R. eburnea</em> (4)</td>
<td>Range &gt;32 2 to &gt;16 &gt;32 2 to &gt;16 8–32 0.06–0.25 0.015–0.06</td>
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<tr>
<td><em>R. piperina</em> (8)</td>
<td>Range &gt;32 0.5–2 &gt;32 0.5–1 1 0.03–0.25 0.015–0.06</td>
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<tr>
<td><em>R. cyclindrospora</em> (2)</td>
<td>Range 0.5 0.25 0.125–0.25 ≤0.03 0.125–0.25 0.125–0.25 0.06</td>
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<tr>
<td><em>R. brevistipitata</em> (2)</td>
<td>Range 1.0 0.25 0.5 0.03–0.25 ≤0.06–0.125 0.125–0.25 0.06–0.125</td>
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</tbody>
</table>

and have so far not been described as pathogens causing invasive fungal infections.

In summary, we found high isavuconazole MICs for isolates of the *R. argillacea* species complex, indicating that this agent may not be a viable treatment option for invasive infections with this emerging fungus. However, future *in vivo* studies are warranted to verify the *in vitro* data obtained in the present study.

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REFERENCES


