

**TITLE:** DISCOVERY OF NEW ANTI-*Sporothrix* COMPOUNDS IN THE PATHOGEN BOX

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**ABSTRACT:**

The search for active molecules against pathogenic fungi is paramount, as current antifungal options for clinical use are limited, especially against dimorphic fungi such as *Sporothrix* species. The *Sporothrix* genus includes important human pathogens that cause sporotrichosis, a hyperendemic mycoses in Brazil. In this work, we screened the Pathogen Box chemical library (Medicines for Malaria Venture (MMV), Switzerland) to identify active compounds against *Sporothrix brasiliensis*, the main sporotrichosis agent in Brazil. The Pathogen Box (<https://www.pathogenbox.org/>) contains 400 compounds with demonstrated activity against several etiological agents of neglected tropical diseases. This library contains new molecules and known compounds with repurposing potential. Firstly, we screened the 400 Pathogen Box compounds for their ability to inhibit *Sporothrix* growth at 1  $\mu$ M. Yeasts ( $0.5 \times 10^5$  ufc/ml) of the reference isolate *S. brasiliensis* CBS 133006 were incubated with compounds in the RPMI medium (supplemented with 2 % glucose and buffered to pH 7.2 using 0.165 M MOPS) for 48 h, at 35°C and 5% CO<sub>2</sub>. Fungal growth was evaluated by visual inspection in an inverted light microscope and quantified by spectrophotometric reading at 492 nm. Only thirteen compounds were able to inhibit growth as itraconazole ( $p < 0.05$ ), inducing at least 70% inhibition. Between these compounds, five are new molecules and therefore they were selected to determination of minimum inhibitory concentration (MIC). MIC values were determined for reference strain, two human strains and two feline-borne strains. MIC was determined using broth microdilution technique described in Clinical and Laboratory Standards Institute protocols M27-A3, with minor modification for use with *Sporothrix* spp. yeasts. According MIC values, the compounds MMV687807 and MMV102872 were the most active, with MIC ranging from 0.125  $\mu$ M to 0.25  $\mu$ M and mean of 0.17  $\mu$ M. MIC of itraconazole also exhibited mean of 0.17  $\mu$ M. Ours results indicate that these two compounds have a good anti-*Sporothrix* activity and represents attractive molecules for further antifungal drug development.

**Keywords:** *Sporothrix brasiliensis*, Pathogen Box, antifungal discovery

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