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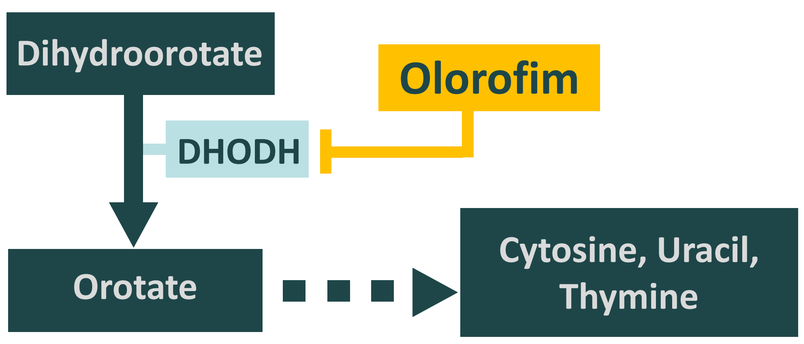
Olorofim is potent against *M. mycetomatis* – most common eumycetoma causative agent

The current treatment for eumycetoma consists of prolonged itraconazole therapy and surgery. However, with 25-50% recurrences, 2.8-25% amputation and an overall 30% treatment success rate, there is an urgent need to find more effective drugs to treat **eumycetoma**.

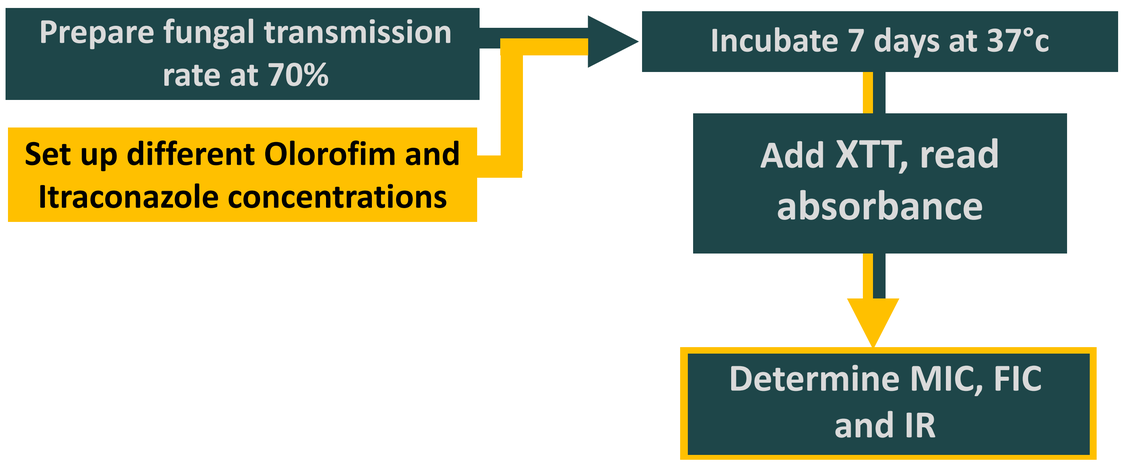
Olorofim (F901318) is a novel antifungal drug belonging to a new class of antifungals called **Orotomides. Orotomides** were discovered in 2015 and act by inhibiting pyrimidine biosynthesis. They cause reversible inhibition of **dihydroorotate dehydrogenase (DHODH),** an enzyme that catalyses dihydroorotate to orotate. This results in an inhibition of fungal growth. Oloforim is found to be effective against *Aspergillus, Fusarium and Penicillium species.*



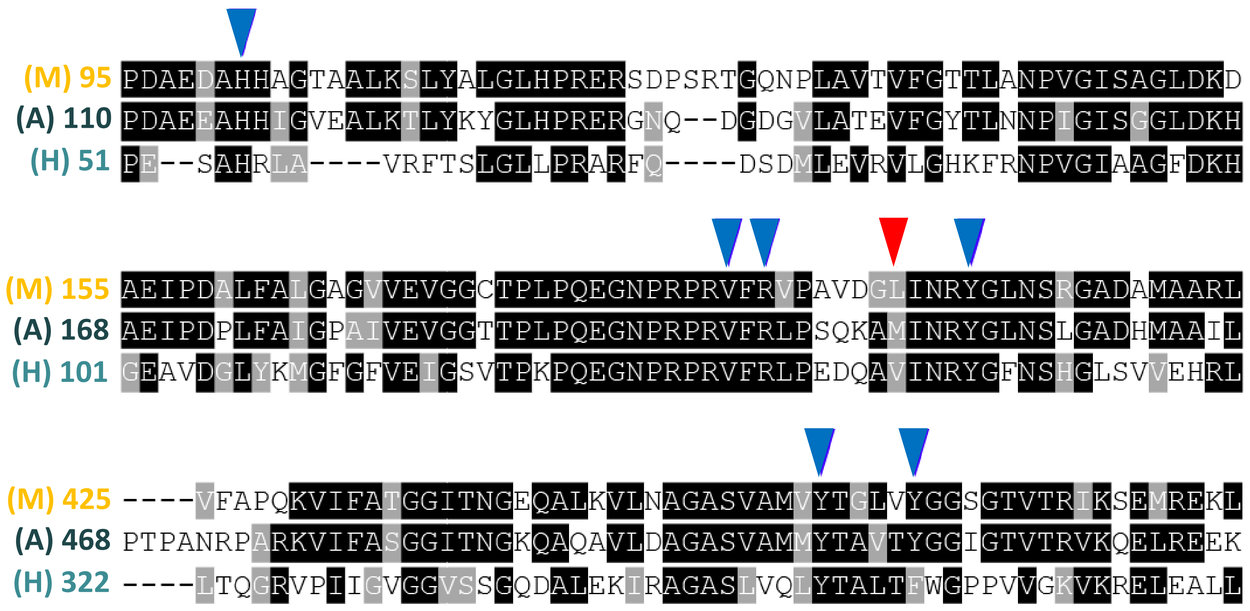
Olorofim is included in the **Pandemic Response Box** by **Medicines for Malaria Venture (MMV).** We are currently testing the Pandemic Response Box under our open source MycetOS project. For more information and discussions, please visit our MycetOS page (scan QR code below).

Aim: To determine the activity of **Olorofim** against *Madurella mycetomatis* – the most common causative agent of eumycetoma by *in silico* comparison and *in vitro* susceptibility testing. Also to investigate the *in vitro* interaction between olorofim and itraconazole to *M. mycetomatis.*

Materials and method: Minimal Inhibitory Concentration (MIC), MIC_{50}, MIC_{90}, fractional inhibitory concentration (FIC) and the interaction ratio (IR) for olorofim and itraconazole to *M. mycetomaatis* were determined. Itraconazole was used as a comparator antifungal agent.

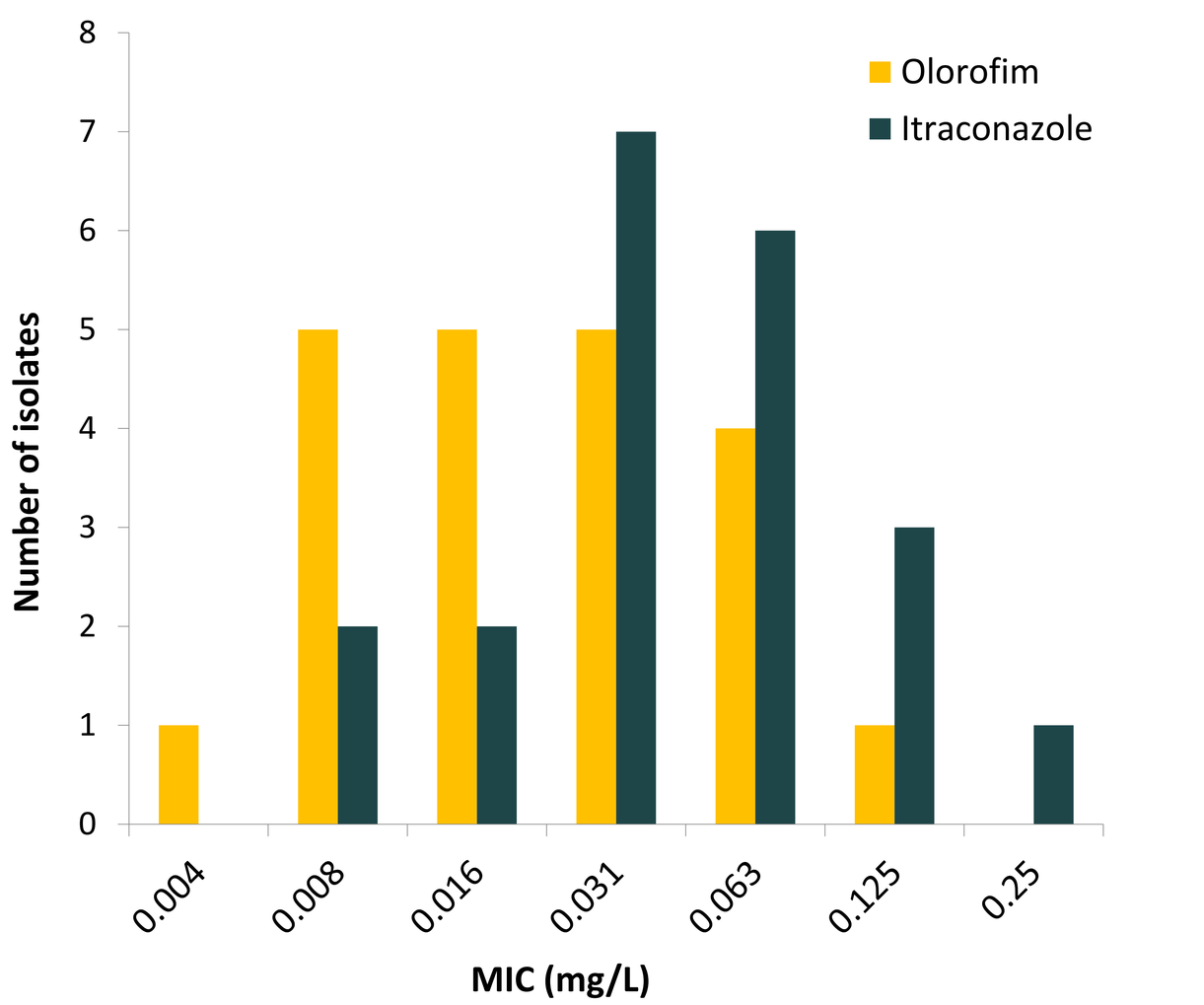


***M. mycetomatis* , *A. fumigatus* and Human DHODH amino acid sequence**



M. mycetomatis and *A. fumigatus* share 6 out of 7 predicted binding residues in their DHODH indicating susceptibility to olorofim. Arrow represent amino acid residues predicted to be important for olorofim binding. Blue = identical. Red = different.
M = *M. mycetomatis* **A = *A. fumigatus*** H = *Homo sapiens*

***In vitro* susceptibility of *M. mycetomatis* to Olorofim and Itraconazole**



MICs range from <0.004 to 0.125 mg/L. Olorofim MICs were consistently one-dilution step lower compared to Itraconazole.

***In vitro* susceptibility and interaction of Olorofim, Itraconazole and both drugs combined**

Antifungal agents (mg/L)	Olorofim	Itraconazole	Combined
Median	0.0156	0.0312	-
MIC range	0.0039 – 0.125	0.0078 – 0.25	-
MIC_{50}	0.015	0.031	-
MIC_{90}	0.06	0.125	-
MIC_{mm55}	0.004	0.25	-
FIC	-	-	3.2 (I)
IR	-	-	0.91 (I)

*Abbreviations: I, Indifferent; FIC, Fractional inhibitory concentration ; IR, Interaction ratio.

Findings: Olorofim inhibits the growth of *M. mycetomatis.* Combining olorofim and intraconazole resulted in indifference. The next step will be to study the efficacy of olorofim and possible itraconazole combination to *M. mycetomatis* in an *in vivo* model.

MycetOS : Open access

An Open Source project aiming at discovering new medicines for the treatment of eumycetoma. The purpose of this project is to open up and gather community expert on this subject in order to progress discovery efforts through community-driven in-kind scientific contributions. All data and ideas are freely shared, and anyone may participate as long as an open approach is held, and that there will be no patents.

We have started an online discussion platform on github (https://github.com/OpenSourceMycetoma) and you can also reach us on twitter (https://twitter.com/MycetOS).

MycetOS Open Source Drug Discovery for Mycetoma

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