
MycetOS
Open Source
Drug Discovery
for Mycetoma

Erasmus MC
University Medical Center Rotterdam

MycetOS
Open Source Drug Discovery for Mycetoma

Using the MycetOS approach to pinpoint chemical properties of fenarimols for *in vivo* efficacy in *Madurella mycetomatis* mycetoma

Wilson Lim,

Youri Melse, Mickey Konings, Hung Phat Duong, Kimberly Eadie, Ahmed Fahal, Benoît Laleu, Benjamin Perry, Matthew H. Todd, Jean-Robert Ioset, Wendy W.J. van de Sande

6th International Conference on Mycetoma
17th February 2019
Khartoum, Sudan

PLOS | NEGLECTED TROPICAL DISEASES

Addressing the most neglected diseases through an open research model: The discovery of fenarimols as novel drug candidates for eumycetoma

Wilson Lim, Youri Melse, Mickey Konings, Hung Phat Duong, Kimberly Eadie, Benoît Laleu, Benjamin Perry, Matthew H. Todd, Jean-Robert Ioset, Wendy W. J. van de Sande

Open Source Mycetoma (MycetOS)

MycetOS:

The MycetOS project was set up in 2017 to discover and study molecules and compounds that are effective against *Madurella mycetomatis.*

Disappointing treatment:
Itraconazole - $300 or more a month
Patient average income $60 a month
Even so, Itraconazole often does not always work

There is an urgent need of a new drug to treat eumycetoma caused by *M. mycetomatis.*

Pathogen and Stasis Box

Pathogen and Stasis Box:

MMV Medicines for Malaria Venture

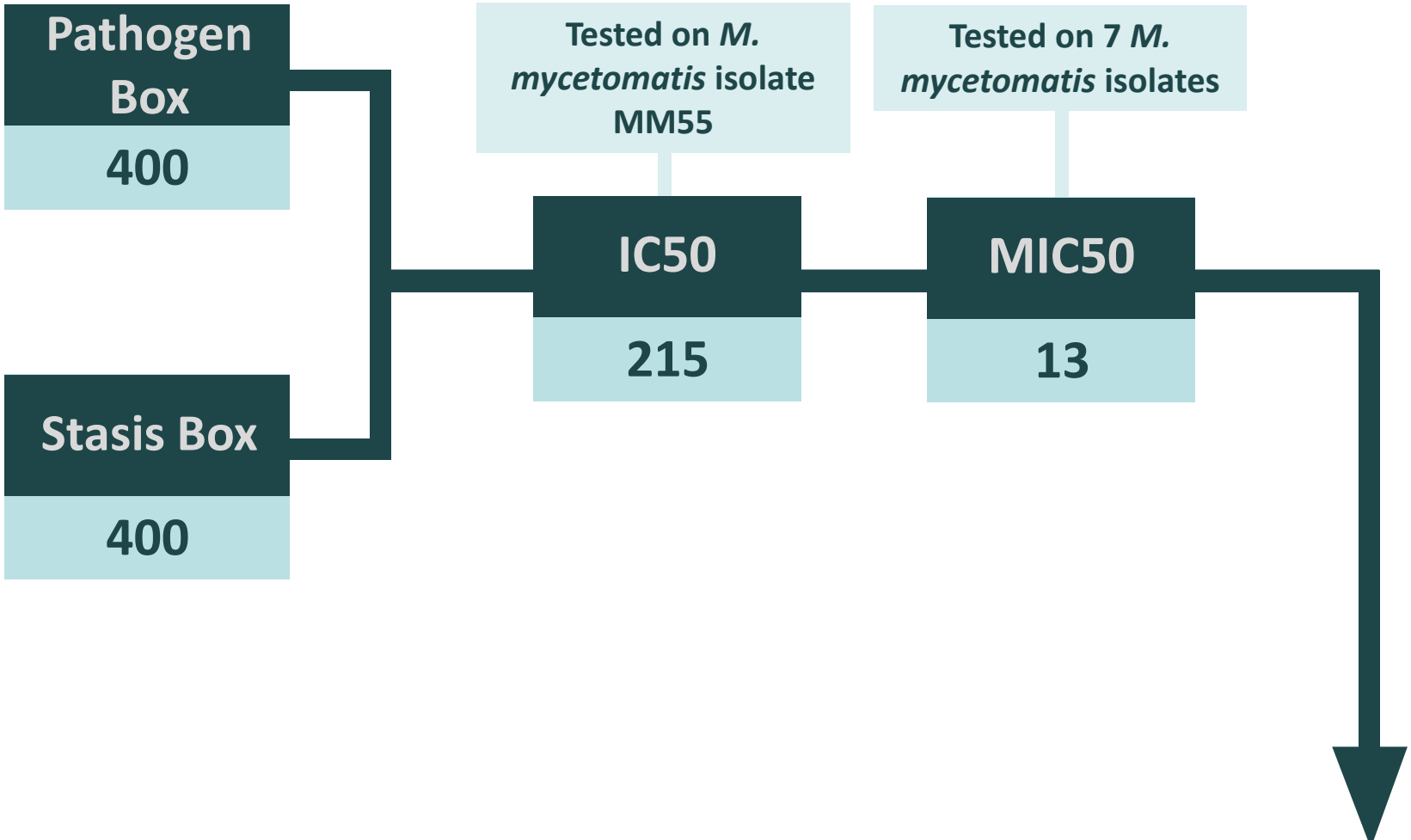
The **Pathogen Box** contains 400 diverse, drug-like molecules known to be active against pathogens causing tropical and neglected diseases.

The **Stasis Box** consists of 400 compounds selected by medicinal chemistry experts which have entered preclinical or clinical development but have been discontinued.

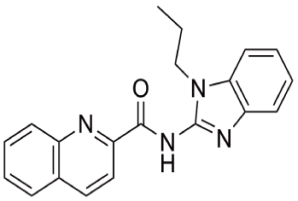
Both boxes are available **free of charge** by the **Medicines for Malaria Venture (MMV).**

In return, researchers are asked to share any data generated in the public domain within 2 years, creating an open and collaborative forum for infectious disease drug research.

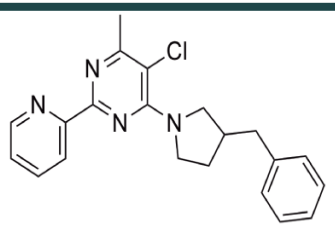
In vitro drug discovery studies



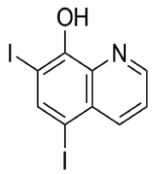
The 13 compounds that worked against *M. mycetomatis in vitro*



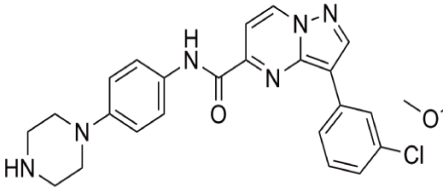
8
MMV1030799



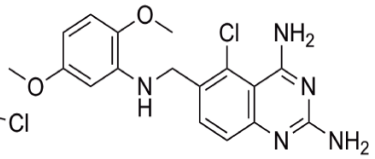
8
MMV659004



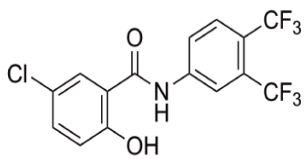
8
MMV002817
iodoquinol



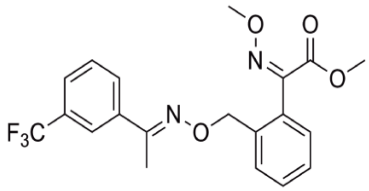
4
MMV022478
BF00174106
CHEMBL534797



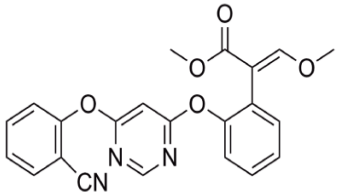
2
MMV675968
BF00174104
CHEMBL88430



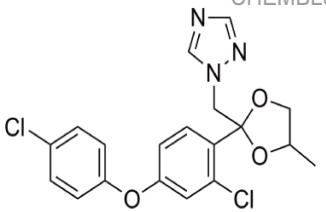
2
MMV687807
BF00174105



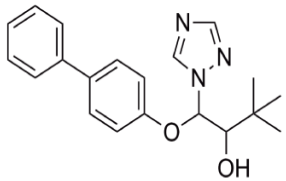
0.25
MMV688754
Trifloxystrobin



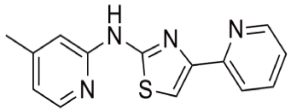
0.06
MMV021057
Azoxystrobin



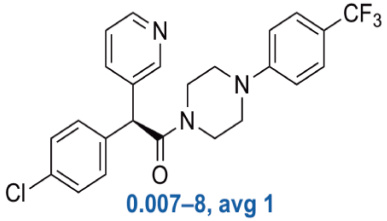
0.06
MMV688943
Difenoconazole



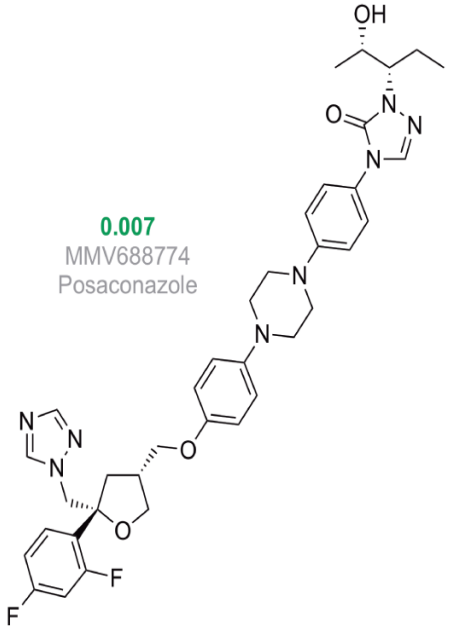
0.06
MMV688942
Bitertanol



0.25
MMV006357
(from *Stasis Box*)



0.007–8, avg 1
MMV689244, EPL-BS1246
FENARIMOL ANALOG



0.007
MMV688774
Posaconazole

In vivo in Galleria mellonela larvae model

Toxicity in larvae

10

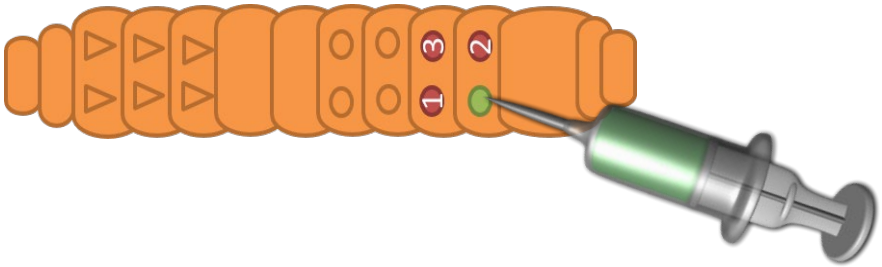
0.2, 2 or 20µM

***In vivo* larvae model**

10

Galleria mellonela (wax moth) larvae model

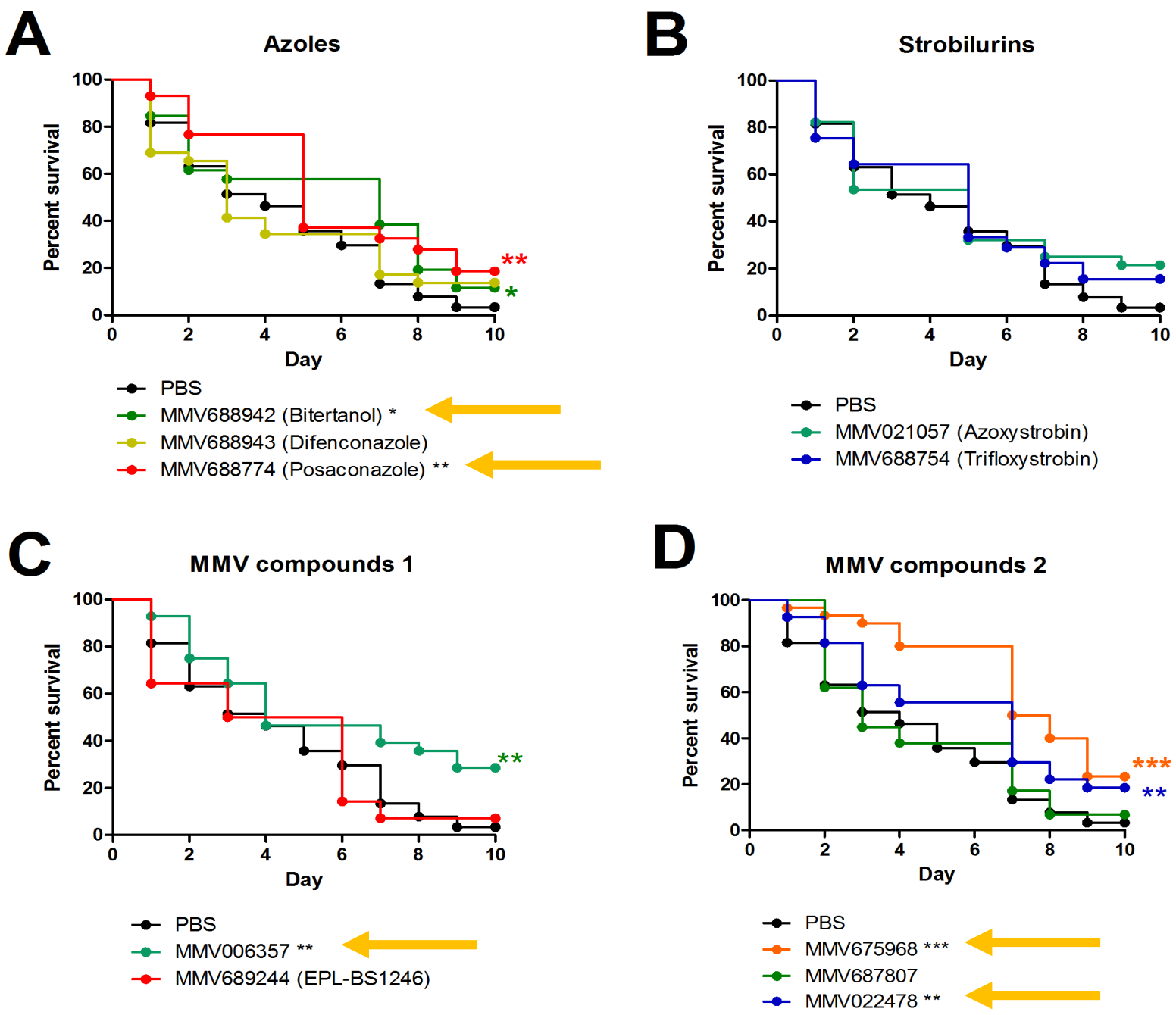
G. mellonela larvae was infected with *M. mycetomatis* and their survival was monitored over 10 days.



Fungal load: 4mg per larvae

Treatment: 20µM

Administration: 4, 28 and 52 hours post infection

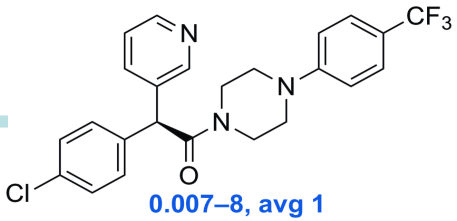

A
Azoles
Percent survival
Day
PBS
MMV688942 (Bitertanol) *
MMV688943 (Difenconazole)
MMV688774 (Posaconazole) **
B
Strobilurins
Percent survival
Day
PBS
MMV021057 (Azoxystrobin)
MMV688754 (Trifloxystrobin)
C
MMV compounds 1
Percent survival
Day
PBS
MMV006357 **
MMV689244 (EPL-BS1246)
D
MMV compounds 2
Percent survival
Day
PBS
MMV675968 ***
MMV687807
MMV022478 **

The Fenarimols

MIC50

13

Fenarimol analogue



0.007–8, avg 1
MMV689244, EPL-BS1246
FENARIMOL ANALOG

Fenarimol analogues

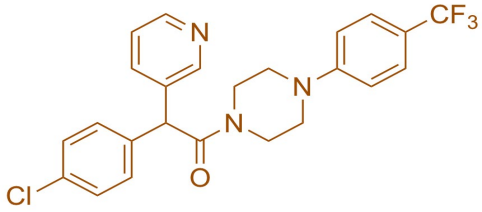
35

MIC50

4

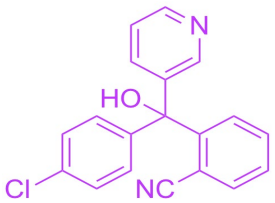
***In vivo* larvae model**

4

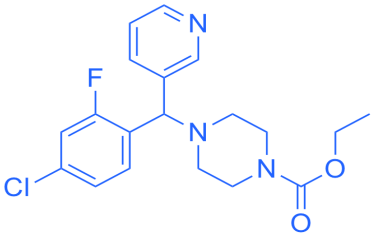


0.63, 0.94, 4
EPL-BS1025 (*rac*)

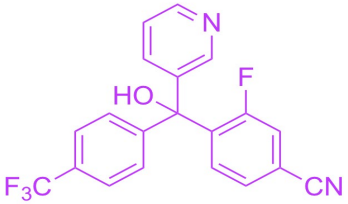
1.53, 2.89, 4
EPL-BS1246 (*S*)



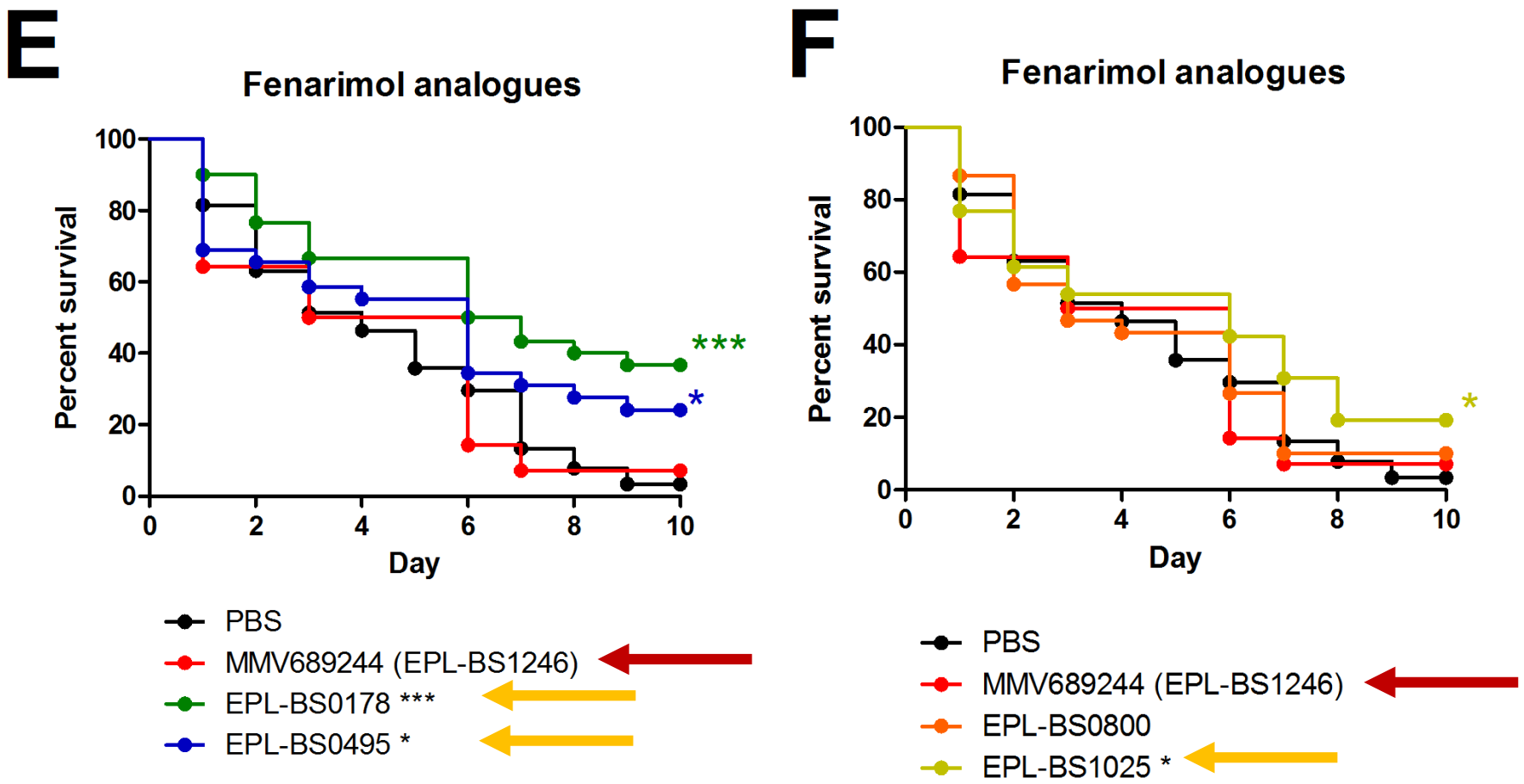
1.25, 1.8, 8
EPL-BS0178

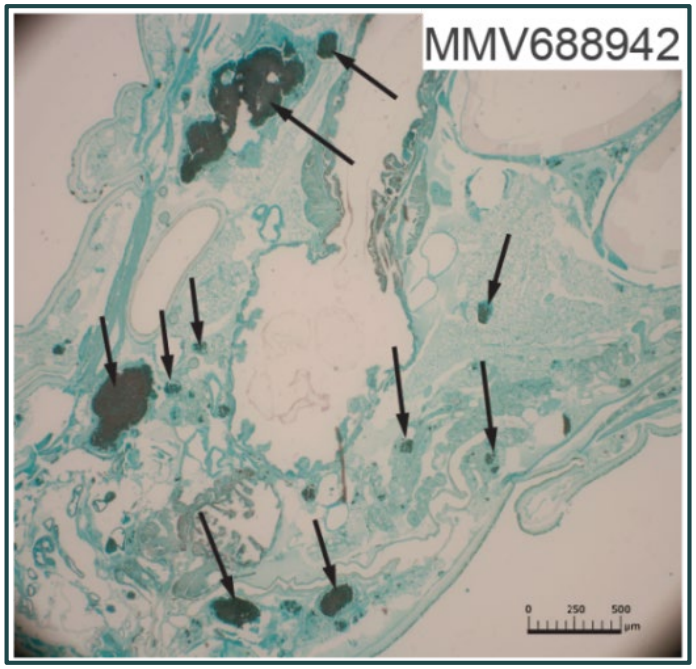


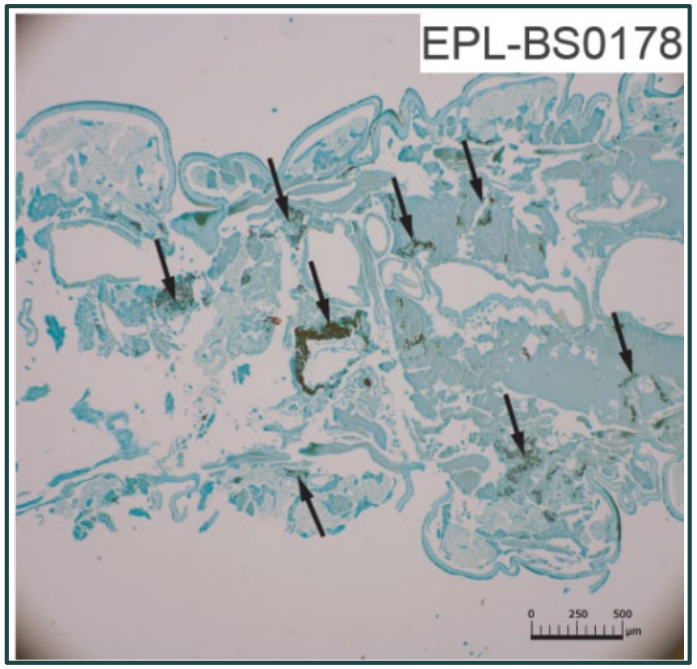
0.28, 0.46, 4
EPL-BS0495

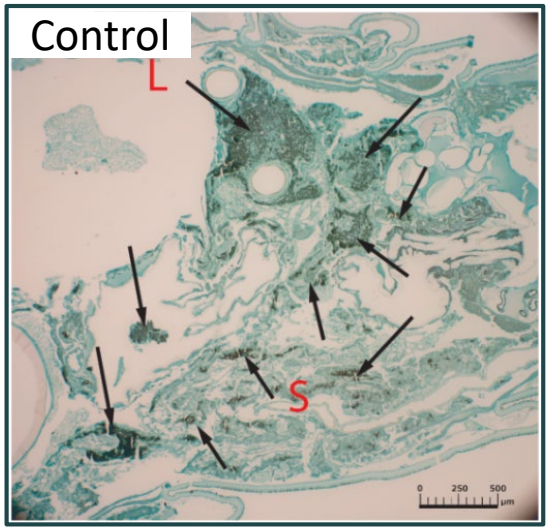


0.58, 0.87, 4
EPL-BS0800


E
Fenarimol analogues
Percent survival
Day
100
80
60
40
20
0
0
2
4
6
8
10
***
*
PBS
MMV689244 (EPL-BS1246)
EPL-BS0178 ***
EPL-BS0495 *
F
Fenarimol analogues
Percent survival
Day
100
80
60
40
20
0
0
2
4
6
8
10
*
PBS
MMV689244 (EPL-BS1246)
EPL-BS0800
EPL-BS1025 *







Histological findings:

Smaller and lesser grains observed in treated larvae compared to the control group.

MycetOS: Open access

MycetOS : Open access

We have adopted an Open Source approach for this project for the purpose of opening up to the wider community.

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.

Data from this project is freely available from the Mycetoma working group, and we have started online discussions on Github so anyone that is interested to join in MycetOS can do so. Together we exchange ideas and discuss to bring MycetOS further.

So far on MycetOS project:

Discovered several molecules and compounds that is effective against *M. mycetomatis in vivo and in vitro.*

They include the azoles, strobilurins and other MMV compounds.

Fenarimols is a good candidate for a novel antifungal.

2 other classes of antifungals has been proposed via the open community discussions. We are now looking for drug libraries of these drug candidates to test.

Next, on Fenarimols !

Fenarimols is a good candidate for a novel antifungal.

Fenarimol is a fungicide normally used in plants. It falls within the triazole group and works by inhibiting the fungus's biosynthesis of ergosterol.

Now, with the ideas that were contributed and discussions that we have had on Github, we have selected 100 out of 800 additional fenarimol analogues to further test.

Some of these analogues share similar properties to the potent fenarimol analogue tested earlier in the MycetOS project.

Screening *in vitro* and *vivo* will be expected to start soon

MycetOS depository and discussions

We have deposited all data associated with this work in an online database (**http://tinyurl.com/MycetomaMols**).

We started an online discussion area on two websites to gather community expertise (**https://github.com/OpenSourceMycetoma**).

We have also started a social media account for community use and outreach (**https://twitter.com/MycetOS**).

These resources constitute ***Open Source Mycetoma*** (**MycetOS**).

DNDi
Drugs for Neglected Diseases *initiative*

MYCETOMA: NEW HOPE FOR NEGLECTED PATIENTS?

Using innovative science to find new drug candidates for mycetoma

Collaborative approaches in drug discovery

SEARCH FOR NEW CHEMICAL ENTITIES THROUGH AN OPEN SOURCE PROJECT

In 2018, the University of Sydney, Erasmus MC, and DND*i* launched the Mycetoma Open Source project (MycetOS), which uses an Open Pharma[13] approach to discover new drug candidates (new chemical entities, or NCEs) for eumycetoma using open-access data and collaborative methods.

With this radically open approach, it is hoped that MycetOS will drive the advancement of promising new chemical compounds targeting *Madurella mycetomatis*, the main cause of eumycetoma.

The project, which is not owned or led by any individual or research institute, will progress drug discovery efforts through community-driven, in-kind scientific contributions, and a robust, fully transparent online presence. Anyone interested can participate by following the community's interactions on Twitter at @MycetOS. All ideas and results will be published immediately in real time to an open-access database.

MycetOS @MycetOS #OpenScience

PURPOSE

Fungal mycetoma: Neglected disease that leads to disability and stigma and has no effective treatment

Develop new medicine to treat fungal mycetoma (eumycetoma) using an Open Pharma approach

CONCEPT

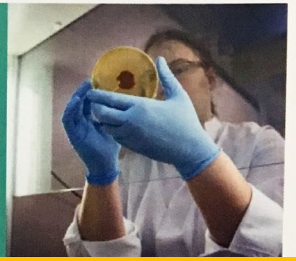
Virtual community: Invite the scientific and global health community to contribute

Open access database: Drive lead optimization of compounds targeting *Madurella mycetomatis*

OPEN

Free of intellectual property constraints

> "While MycetOS merely starts a process of discovering potential new chemical entities for eumycetoma, we invite anyone interested to identify how they might contribute and participate as an equal partner in this search for a new treatment for this most neglected of tropical diseases."
>
> Dr. Wendy van de Sande, Associate Professor, Erasmus MC



Contact:
Wendy van de Sande
w.vandesande@erasmusmc.nl

Wilson Lim
w.lim@erasmusmc.nl

Erasmus MC, Department of Medical Microbiology and Infectious Diseases, Rotterdam, The Netherlands

PLOS NTD

github

Twitter