# TARGETED-INHIBITION OF M. MYCETOMATIS

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## Context

Mycetoma can be caused by the fungi eumycetoma in tropical/subtropical soil or water of developing countries. It usually enters through a person's foot resulting in chronic mutilating disease. Current anti-fungal drugs have low efficacy for eumycetoma. Pharmaceutical laboratories have a low financial incentive for this fungal research, making it a neglected tropical disease. Therefore, MycetOS attempts to use open-source drug discovery methods to combat this problem.

## Question

We are using Datawarrior to visualise and analyse compounds and employ structural activity relationships to help find future cores and substitutes to treat eumycetoma.

## Method

Datawarrior is a database platform that performs cheminformatic algorithms to visualise activity cliffs. The activity cliffs show the relationship between biological activity and molecular structure in aiding to discover new potential treatments for targeting M.mycetomatis, the dominant agent that causes fungal mycetoma (eumycetoma).

- Our main method of analysis was using similarity trees of the three descriptors as it was much easier to match structure and flexibility to inhibition activity in comparison to the 2D and 3D plots.
- The similarity trees were used to find the cores through identification and analysis of interesting groupings of molecules, these being compounds with similar structures, but vastly different activity levels.
- Once an interesting core was found the molecules were listed in order of inhibition, with similar structural features being identified to see how they related to the activity.
- If there was a certain element which consistently resulted in high growth activity it was regarded as inactive, and if there were elements which consistently resulted in low growth activity they were regarded as active cores.

FragFP: The default descriptor of Datawarrior, and quickly connects compounds by their structural similarity in the 512 predefined structures in the dictionary.

Skelsphere: Compares molecules' similarity through spheres of connected atoms while taking into account the stereochemistry of the molecules.

Flexophore: A practical and powerful method in predicting 3D-pharmacophore similarities and allows checking for any compatible protein-binding behavior by taking the molecular flexibility into account.

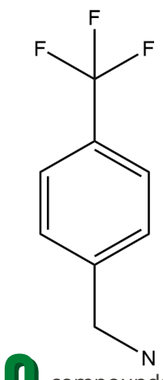
## Results/ Discussion

### Inactive core

- For the first inactive core: FragFP and Flexophore have very disconnected similarity trees, whereas for Skelsphere it has a highly connected similarity tree indicating a structural and biological relationship. This result implies that the inactivity is mainly due to structural reasons rather than flexibility. The disconnectivity shown in FragFP is due to the 512 predefined structures.
- For the second inactive core: All three descriptors show a high level of connection in the similarity trees. This links the structure and flexibility of this motif to the low biological activity for the Sydney group.
- For the third inactive core: FragFP and Skelsphere show excellent connectivity in the similarity trees, indicating a relationship between the structure and poor activity. The Flexophore descriptor shows little connectivity in the similarity tree indicating that flexibility is not connected to the inactivity of this motif.

Skelsphere similarity tree of motif 3.

1.



**19** compounds with this core were inactive.

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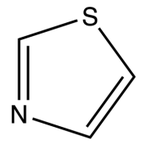

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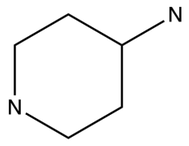
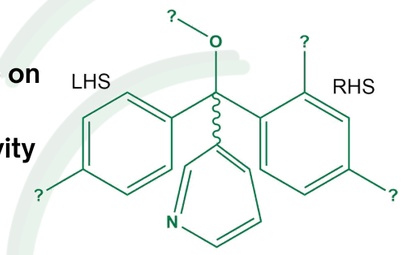


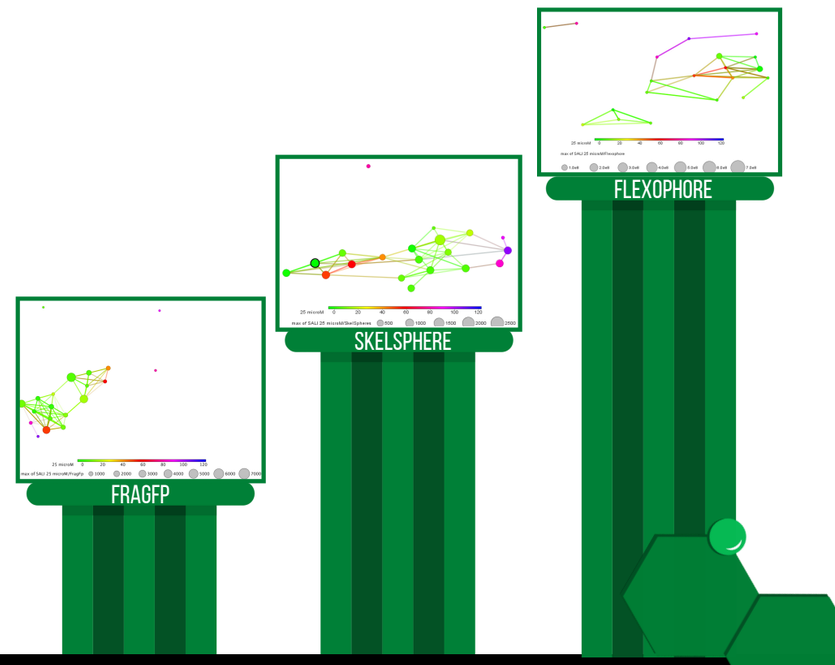
**34** compounds with this core were inactive.

### Active core

- The most beneficial inhibition activity had a very electronegative group on the ortho position of the RHS of the S-active core and a very electronegative group on the para position of the LHS.
- It was also found that the absence of groups or a group with low electronegativity on the para position of the RHS of the S-active core could potentially enhance beneficial inhibition.
- A positive correlation was shown where increasing the electronegativity of an atom attached to the ortho position led to better activity. This relationship might be due to the slight interaction between the halogens and the hydrogen (halogen-bonding), increasing the molecule's stability.




**19** compounds had this core.
**12** were active.
**7** were inactive.




### Descriptors

- The connectivity for all three descriptors shows great connectivity in the similarity tress. This suggests that structure and flexibility play an important role in providing great biological inhibition activity, which reflects our finding above.

## Future Work

<u>Two compounds for future investigation in respect to SSP compound set</u>

A common feature that had diminished the activity of the active compound was changing the 1,6-arrangement of the pyridine group. Building a compound for future investigation would first maintain this 1,6-arranged pyridine property as much as possible.

1. Our first proposed compound kept the 1,6-arranged pyridine and added an azetidine group to the molecule. This is because azetidine-containing compounds have been widely used for drug designs. Hence, it was added to test and see whether this change would function similarly to those other successful azetidine-containing drugs.

2. Second proposed compound was to see whether the electron pair embedded in the ring at the 1,6 position plays a role in changing the activity of the compound. Thus, by replacing the N to O this would help investigate the activity in respect to the electron pair embedded in the ring.

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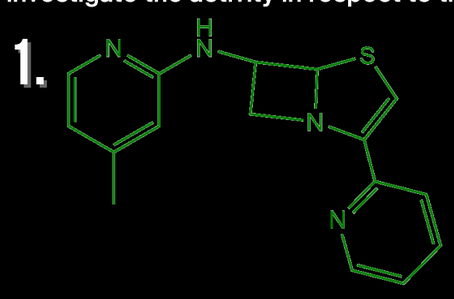

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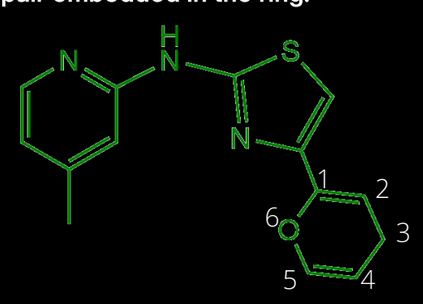

<u>Three compounds for future investigation in respect to the active core</u>

1. A majority of the active core compounds were chiral. Therefore the suggested compound investigates if the enantiomer of one of the compounds holds the same level of activity. The original compound which showed strong activity had a dashed bond which has been replaced by the wedged bond.

2. There was a general trend in which the higher the electronegativity of the atom attached in the ortho position on the RHS resulted in a higher activity of that compound. This may be due to the interaction going on between the hydrogen from the alcohol and the electronegative atom (F & Cl). Thus, by placing the fluorine to the para position (decreasing this interaction), this would help to identify if the ring substitution plays a role in affecting the activity of the compound.

3. This molecule was suggested to see if the trend that a highly electronegative group on the RHS ortho and a highly electronegative group on the LHS para leads to increased inhibition.

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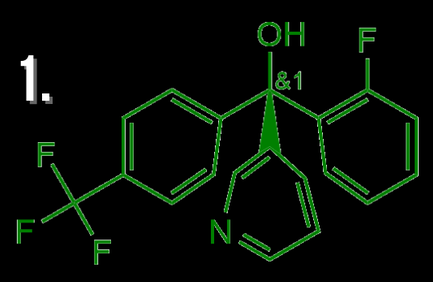

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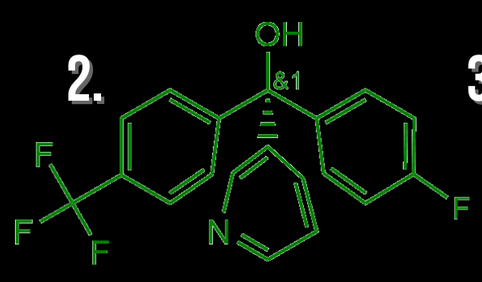

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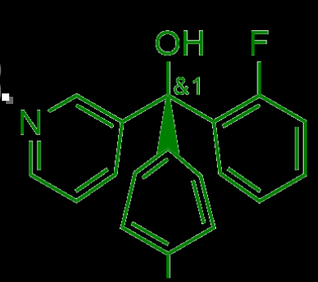

## References

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Reis, C. M.; Reis-Filho, E. G. Mycetomas: An Epidemiological, Etiological, Clinical, Laboratory and Therapeutic Review. Anais Brasileiros de Dermatologia 2018, 93 (1), 8–18.