Hindered Lewis Bases Have Potential as Antifungals for Eumycetoma

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References: 1. Pal, Mahendra & Dave, Pratibha. (2019). Mycetoma: An Infectious Neglected Tropical Devastating Disease. 3. 1-9. 2. Queiroz-Telles, F., Fahal, A. H., Falci, D. R., Caceres, D. H., Chiller, T., & Pasqualotto, A. C. (2017). Neglected endemic mycoses. The Lancet. Infectious diseases, 17(11), e367–e377. https://doi.org/10.1016/S1473-3099(17)30306-7 3. Sabo, Janelle A., and Susan M. Abdel-Rahman. "Voriconazole: A New Triazole Antifungal." Annals of Pharmacotherapy, vol. 34, no. 9, Sept. 2000, pp. 1032–1043, doi:10.1345/aph.19237.

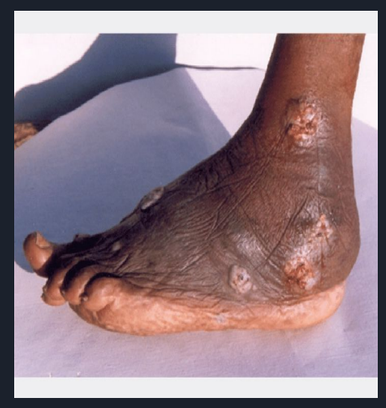


Figure 1. Eumycetoma: A devastating tropical disease.[1]

Context: Mycetoma is a chronic skin infection that causes foot deformity[1] (see fig 1), and neglected tropical disease. The fungal (Eumycetoma) variety is much more difficult to treat due to limited effectiveness of present antifungals, often resulting in amputation. MycetOS is trying to find treatments based on open-source methods and has tested 183 compounds for growth inhibition.

Question: My Aim is to find compound properties that are predictive of antifungal effect using Datawarrior in order to postulate further compounds that are likely to be Eumycetoma-inhibiting.

Methods:
Using PathFp and growth at 0.1M, I constructed a Structure-Activity Landscape Index (SALI - fig 2) to visually represent the activity of related molecules. I paid special attention to two situations. One, where highly active compounds were similar to those of middling or no antifungal effect - 'activity cliffs' which highlighted relevant properties. I also looked at large groups of similar effective compounds as a starting place for active motifs - using the SALI plot to then validate my findings (reasoning that effective sub-structures should work across otherwise dissimilar compounds).

Having found active functional groups, I then looked through various physical properties to check if any were able to explain differences in activity. These included the counts of various heteroatoms and solubility measures.

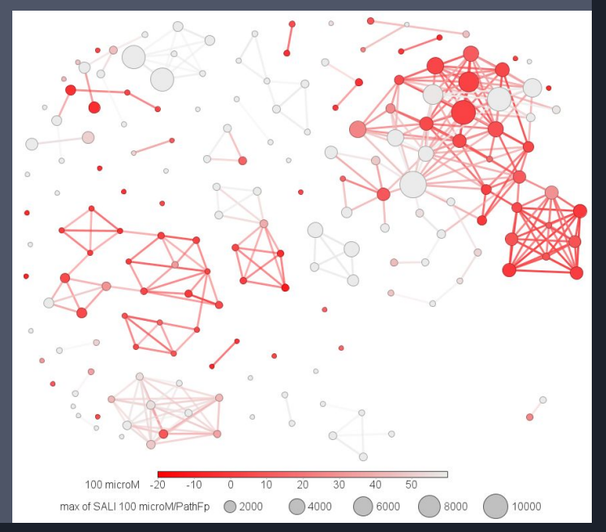
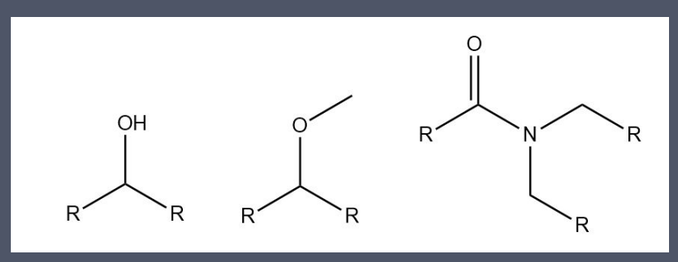
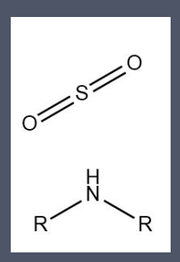


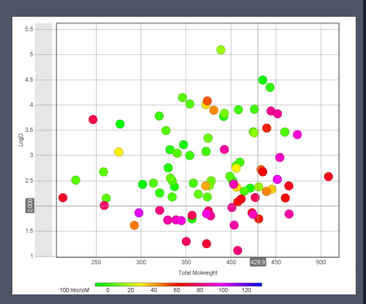
Figure 2. The full SALI plot showing how active and inactive compounds are often related, though multiple exceptions exist.

Results: Activity cliff analysis shows that viable antifungals are generally less polar (more octanol than water soluble), have lower molar masses, and contain hindered nucleophiles.
I found two inactive motifs - any sulfoxides were ineffective, as were most compounds with N-H hydrogens (fig 3 mid - either R could be H). Conversely, hindered oxygens (either as Non-primary alcohols or methyl ethers) and tertiary amides were generally antifungal (see fig 3 left). Of compounds with the latter groups, most but not all are effective. I found compounds with either logD < 2, or Molar mass > ~430 g mol^{-1} generally ineffective, as were those with small R groups.

Figure 3 (Left - Active Cores, middle - inactive groups,
Right - scatter for compounds that include active & exclude Inactive to show effect of molar mass and solubility)

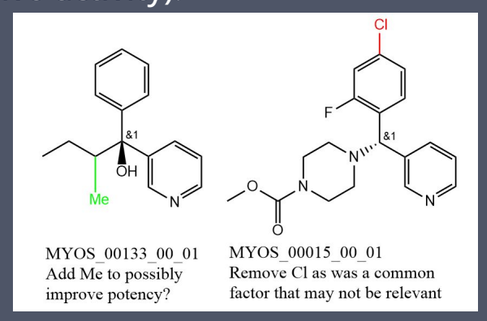






Future Work:
Present treatments for eumycetoma are generally triazoles with similar structures to the tertiary alcohols surveyed.[2] This makes the effective compounds interesting as there are no di or triazoles. Small chemical changes can have outsized effects on medicinal effectiveness, as shown by 'second generation' antifungals.[3] As the current compounds are effective, I would consider working with derivatives of these compounds to find ones that work at lower concentrations potential future work. These compounds (fig 4) have potential for novel antifungal activity as they present perubations on unusual matches to my resulting 'rules', are fairly small and on the more water soluble end (the latter two chosen to promote in vivo activity).

Figure 4 - proposed minor changes to investigate on effective compounds



[I would consider these compounds guidelines for future research as these choices don't consider practical availability and I am not a medicinal chemist.]