Combatting Mycetoma:
Modelling Antifungal Molecular Substrates

Eugene In, Niamh Montgomery, Rachel Seo

Introduction

Mycetoma is a progressive, chronic infection of the skin and subcutaneous tissue from fungus and bacteria.[1] There are limited treatments - and no cure, with only preventative measures aiding chronic symptom management.[1] Thus, mandating research into therapeutics to ameliorate this health endemic.

DataWarrior software analyses the feasibility of enzyme-specific, pharmacoactive compounds[2] against fungal mycetoma. Visualisation, molecular analysis and data management from a library of published databases map molecule derivatives with regarding structural relationships via cheminformatic algorithmic calculations.[2] Herein, this investigation utilises SkelSphere and Flexophore chemical descriptors to explore molecular similarity, serving as computational evidence for potential experimental testing of novel antifungal substrates.[2]
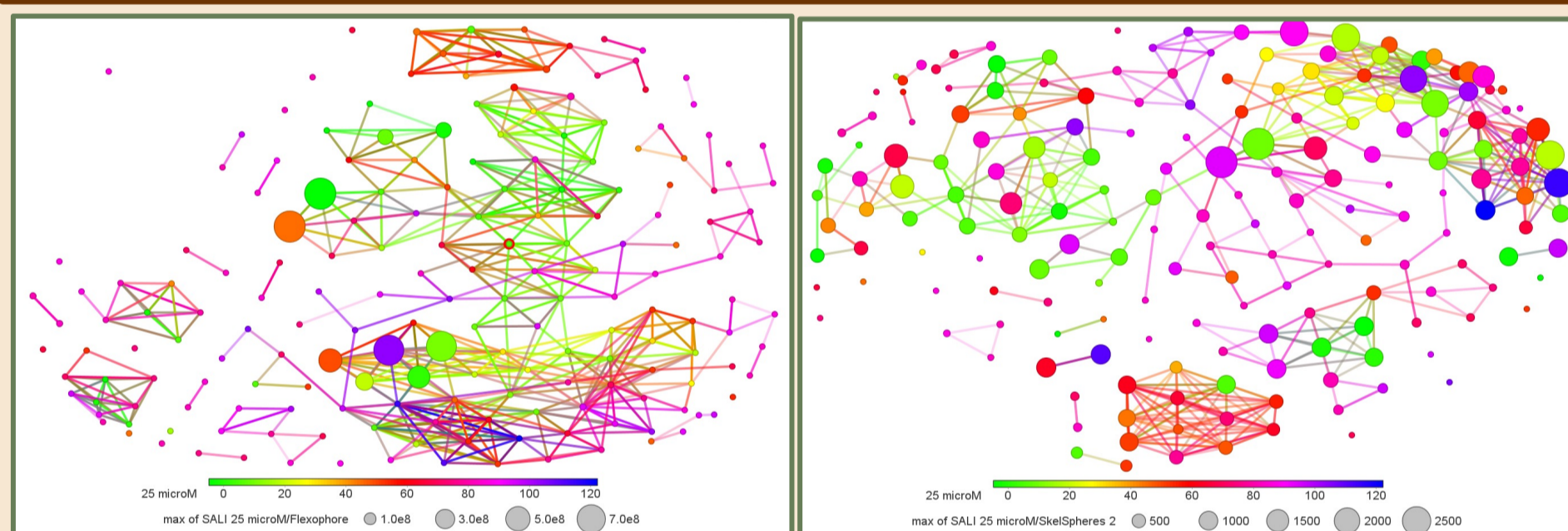

Figure 1. Flexophore (left) and SkelSphere (right) similarity tree plots.

Method

Activity-Cliff analysis utilised SkelSphere and Flexophore chemical descriptors at 25 µM. Structure-activity landscape index (SALI) plots of similarity were constructed, with Activity-Cliff plots for overall delta activity values. Bioactivity from structural differences were isolated from branches of similarity tree plots, identifying general core structural patterns with varying substituent groups. Delta activity plots verified substituent group effects on activity, refining analysis scope.

Analysis at 25 µM was deemed favourable over 100 µM, for small-scale data validity, reliability and reproducibility, in transference of computational data to future experiments. Flexophore (molecular flexibility and pharmacophore similarities) provided distinct patterns in grouping molecular binding activity. Results were primarily derived from Flexphore plots, with SkelSphere (atom connectivity, stereochemistry) activity values confirming general patterns.

Results and Discussion
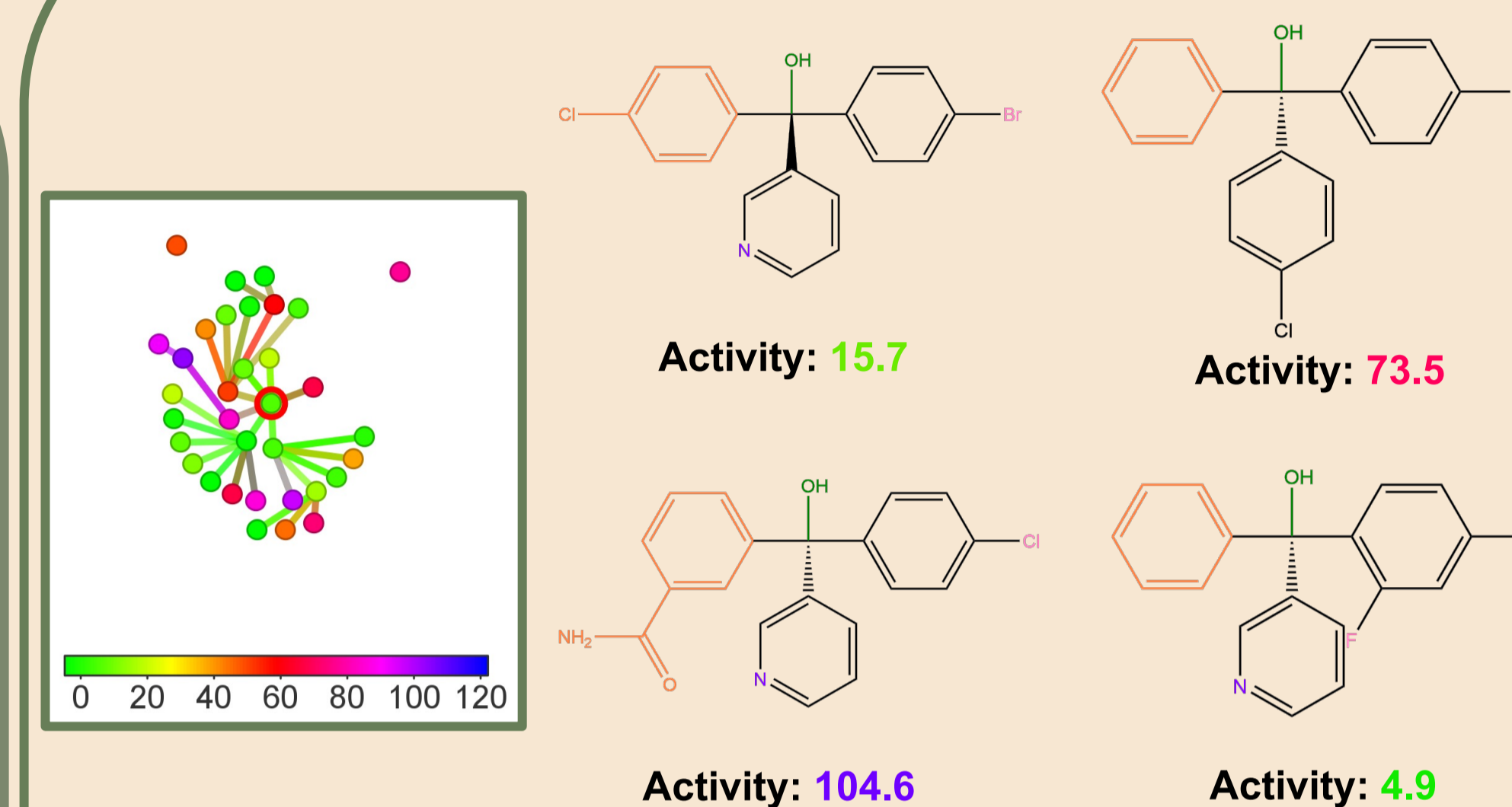
Possible central groups:
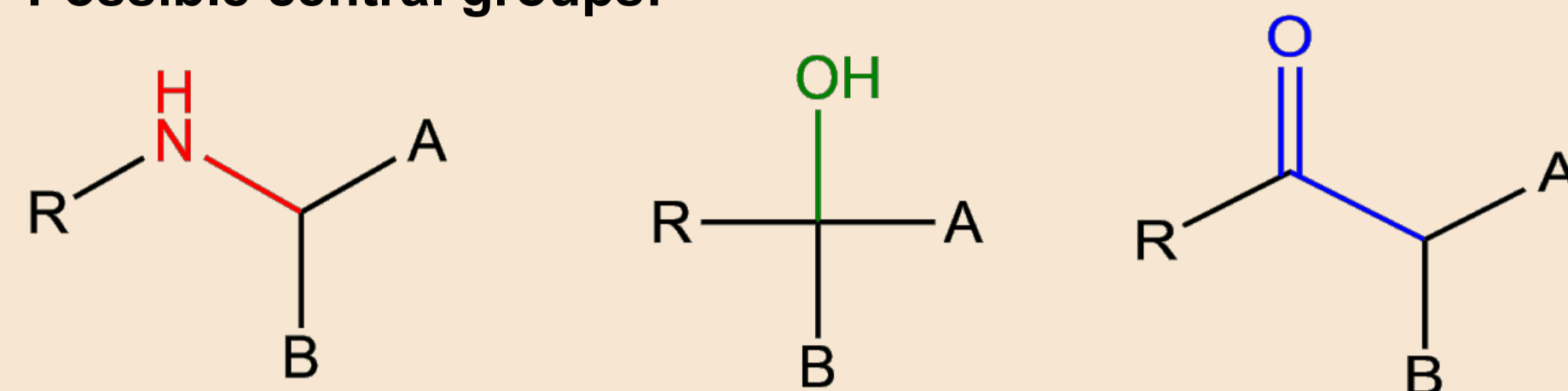
Examples:
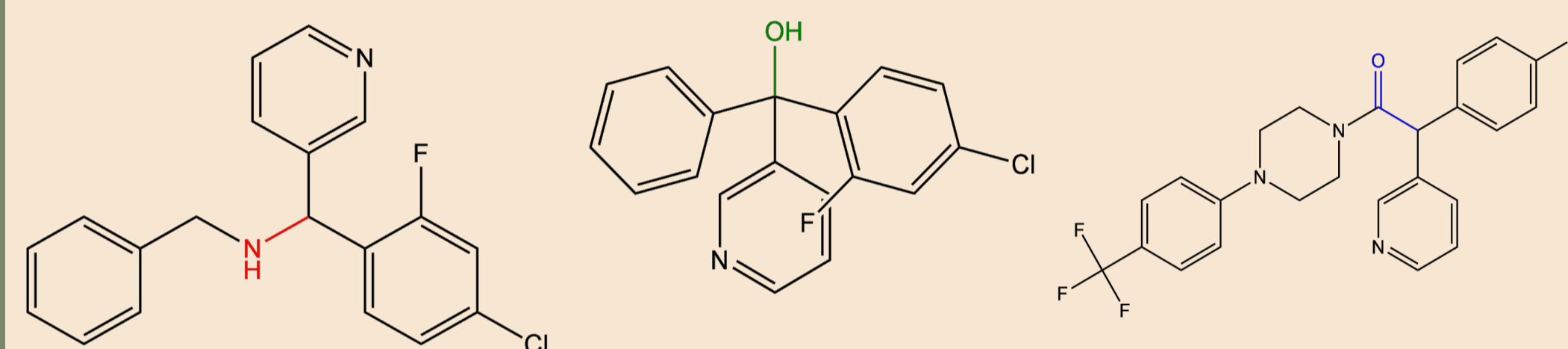
Three central groups were identified. Electronegative hydroxyl, carbonyl and secondary amine groups contain lone pairs. All central groups presented similar bonded substituent groups.
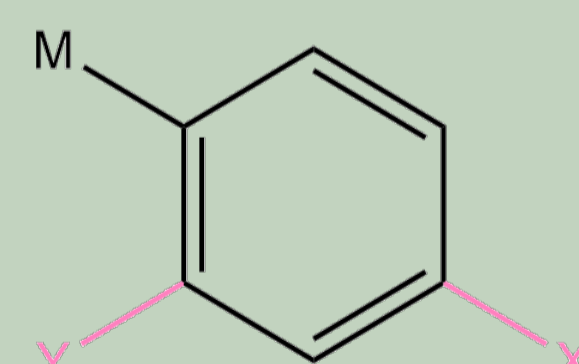
Figure 2. General schematic of central structural patterns from Flexophore and SkelSphere chemical descriptor analysis.

Substituent Groups

	In successful structures of high activity, the 'A' substituent tends to be a substituted phenyl group, with a halogen (X) in the para position, either chlorine, bromine, or -CF$_3$. There is a possible second substitution at the ortho-position (Y), which is usually fluorine. The central group is 'M'.
	The 'B' substituent tends to be a nitrogen containing heterocyclic compound. This almost always included a nitrogen in the meta position, although some molecules had a secondary nitrogen in the second meta position (Z).
The 'R' Group	The 'R' substituent varied the most between molecules. With very little correlation between size, polarity and functional groups. However, in the Flexophore similarity descriptor, it was found that the 'R' group tended to bind well as a 5-6 membered ring, or a small hydrocarbon chain.

Example Flexophore similarity branch:

Activity: **15.7**   Activity: **73.5**
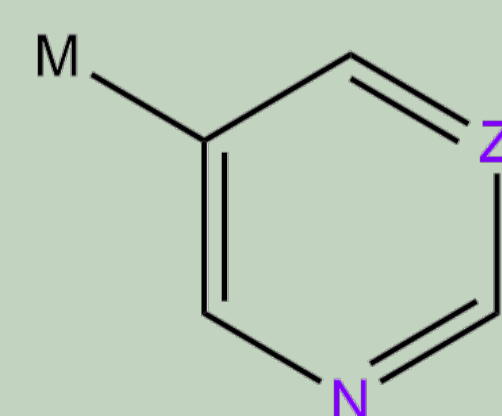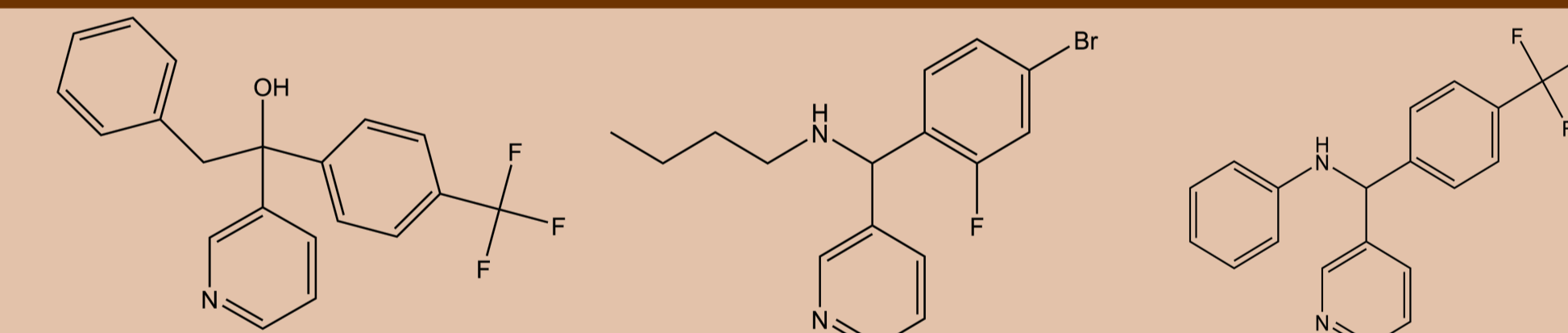
Activity: **104.6**   Activity: **4.9**

All molecules have an OH central group (M), a phenyl substituent with a para-X group (A), with B and R branches. Here, the inclusion of a meta-N-substituted phenyl ring increases binding activity when comparing the top two molecules. Additionally, an (A) group with two substituted X's and a less sterically hindered R group also seems to be favourable.

3 possible future compounds for testing, informed by observations of key central groups and possible substituents. Notably, some molecules in the data set do not follow our identified pattern yet are still successful. These are also of interest for future research, to broaden the pool of drugs to test.

Conclusion and Future Work

Computational analysis of antifungal substrates suggests exploration of molecule derivatives following three major classes of central backbones. Variation by substituent groups presented a spectrum of bioactivities, with Flexophore descriptor most apt for analysing current datasets. Future work in biotoxicity and efficacy of suggested compounds and derivatives are to be conducted. Studies on physical mechanism of molecular outliers may better inform potential biological efficacy of potential therapeutic antifungal substrates. Data arrangement and errors needs to be addressed in the program.

[1] World Health Organization. Mycetoma. https://www.who.int/news-room/fact-sheets/detail/mycetoma (accessed November 13, 2021).

[2] OpenMolecules. DataWarrior User Manual – General Concepts. https://openmolecules.org/help/basics.html (accessed November 13, 2021).