Active Compounds against Eumycetoma

Using DataWarrior to build structure-activity relationships and explore activity-promoting substituents

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Context

Mycetoma is an infectious disease characterised by the destruction of the skin, muscle, and bone. Eumycetoma, a subset of Mycetoma, is caused by fungi. The treatment for Eumycetoma is limited to antifungal medication or surgical excision, both with very low efficacy[1]. The OpenMycetoma group aims to identify possible pharmaceutical compounds to combat Eumycetoma using an open source drug discovery method.

Method

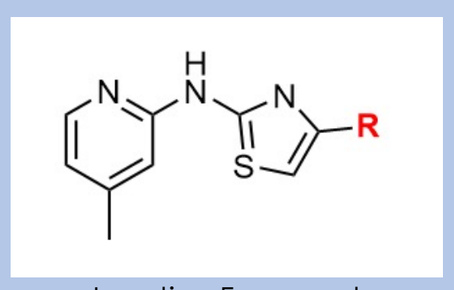
DataWarrior is an open-source, analytical programme that uses chemoinformatic algorithms to visualise and analyse relationships between chemical structures and biological data. From the programme, we focused on two descriptors: Flexophore and Skelsphere. Flexophore allows the prediction of 3D-pharmacophore similarities by analysing the compatibility of protein binding behaviour between two molecules. In contrast, Skelsphere identifies more precise structural differences between the compounds, such as distinguishing and analysing stereoisomers. We analysed the USYD SSP group molecules, led by Kymberley Scroggie, then compared them to other compounds in the database. For the comparison:

- We filtered the USYD SSP group and Kymberley's molecule
- We observed activity relationships and identified any potential trends in the structures using SALI plots
- Focused on the activity/growth of eumycetoma in 25 mM of a synthesised compound. Thus, a more active compound that is better for treatment inhibits the growth of mycetoma and shows a lower activity number.
- Used the similarity tree generated to identify clusters of active structures among all the compounds

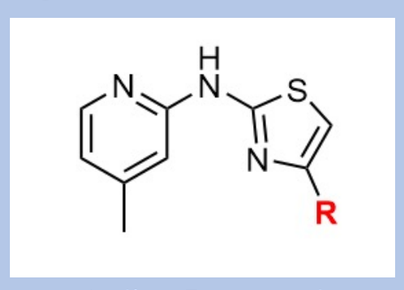
Results and Discussion

KYMBERLY SCROGGIE + USYD SSP STUDENTS COMPOUNDS

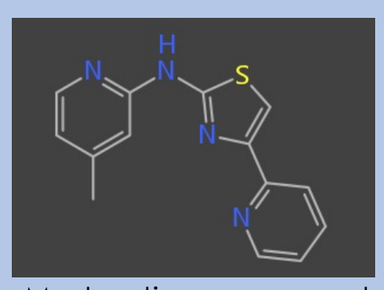
The activity 1 structure (figure 1) had the highest activity of these synthesized compounds. The suspected fragments contributing to the compound's activity or inactivity are identified. The compounds' activity declined when the inactive fragment was used regardless of the R group substituent, while the active fragment's activity was heavily influenced by the R group — a modified phenyl ring in all synthesized compounds. Compared to the most active structure, activity is drastically reduced when the nitrogen atom is moved or removed from its meta position or when electronegative groups are added to the R phenyl ring (as seen from activity 2). Beyond this, there is no apparent, clear relationship between activity and the substituents added or their position. Potentially, activity relates to the charge or electron density within the structure's cavity to promote interactions the causative agent.



Inactive Fragment



Active Fragment



Most active compound activity(25 mM)= 5

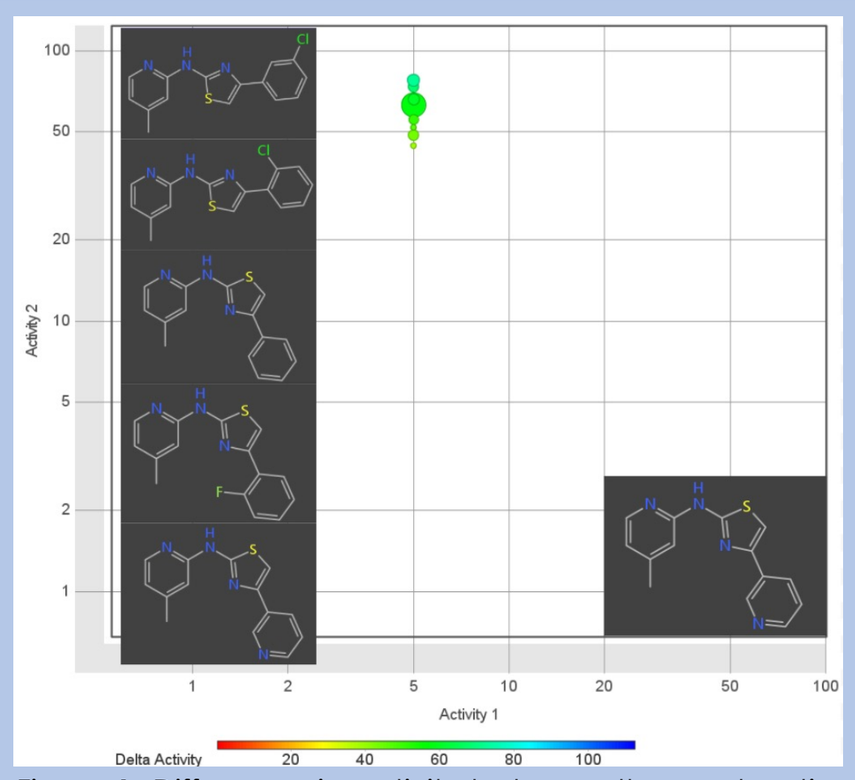
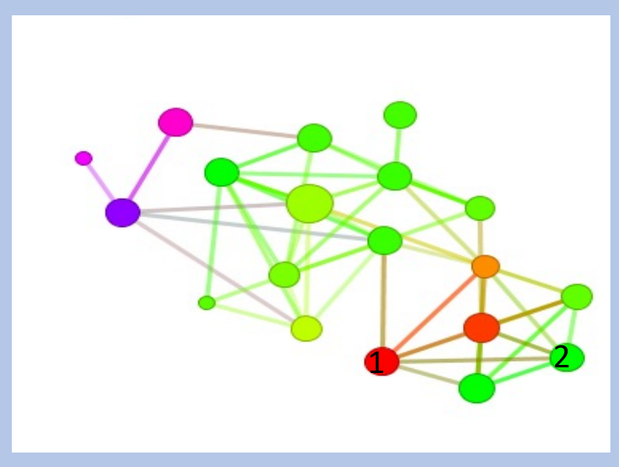
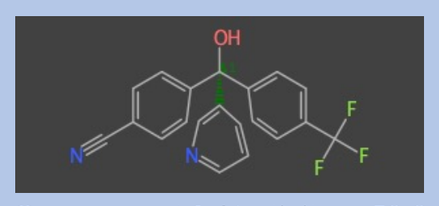


Figure 1: Difference in activity between the most active activity 1 structure (right) and selected activity 2 structures (left) in order of increasing structure activity

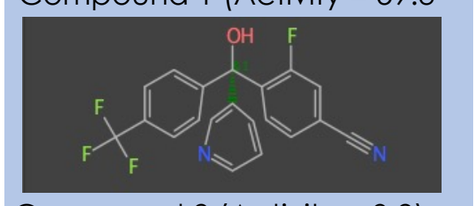
ALL COMPOUNDS

Using the Flexophore Similarity descriptor, a diagram was generated, each compound is represented by a dot with the lines between compounds of similar structure. Surprisingly, all structures in this clump include three benzene rings and an oxygen atom, either as an ether group or an alcohol group. This is regardless of the activity, indicating that this set of compounds likely does not have an active core. Therefore, It is likely that the substituents have influence on the activity of the compounds. In particular, the presence of an allylamine substituent which is present on half of the inactive compounds, but none of the active ones. Of these compounds, 1 and 2 are of particular interest, as they appear to have almost identical structures yet opposite activity. In general, the addition of a fluorine substituent in the meta position of a benzene ring along with another substituent in the para position, increases the reactivity.





Compound 1 (Activity = 59.3



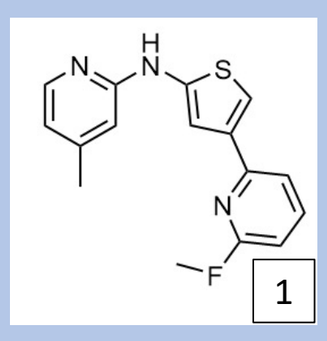
Compound 2 (Activity = 8.2)

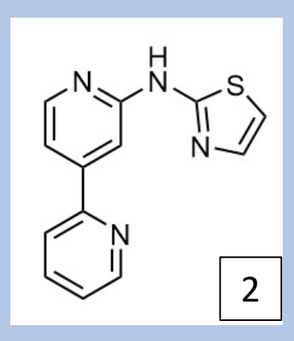
Future work

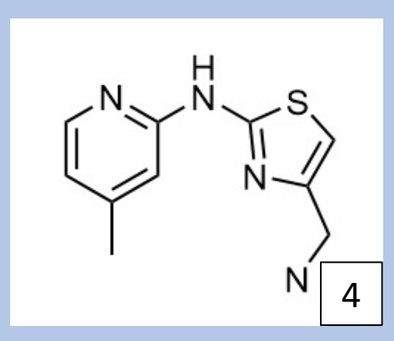
Ultimately, the synthesis of further compounds containing the suspected active core and different substituents aids the comparison of activities to comprehensively classify and identify trends that lead to improved activity. In turn, it is determined what parts of the structure must be conserved as they are important for activity and what parts can be modified to improve bioavailability.

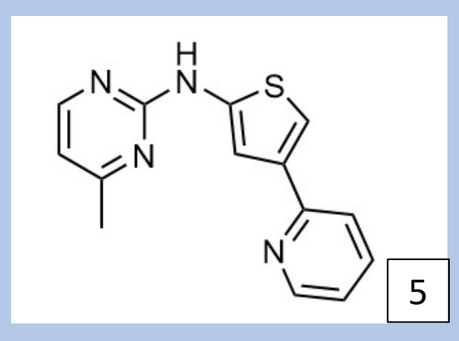
KYMBERLY SCROGGIE + USYD SSP STUDENTS COMPOUNDS

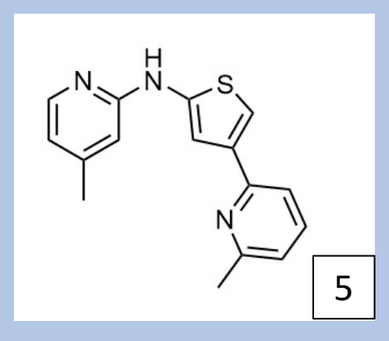
Further investigation should consider the effect of R group substituents of the active core on activity. Changes to future synthesised compounds with the active core can include (1) the addition of methyl groups to electronegative substituents, (2) increasing electron density in different areas by moving the R group around the fragment to understand the mechanism of interaction, (3) generating compounds with the same substituent at each position or different substituents at the same position to compare activity, (4) removing the phenyl ring of the substituent to determine if it, or just N position is important, and (5) adding more nitrogen atoms or hydrocarbon chains to the most active compound.











ALL COMPOUNDS

The analysis of all compounds saw results that contradicted those of the compounds synthesized by Kymberly Scroggie and the USYD SSP students. Instead, adding halogens and electronegative substituents appear to be favourable. Further investigation could be done into the position of the halogen substituent, as well as the incorporation of different groups in place of the oxygen based substituents.

References: 1. Reis, C. M.; Reis-Filho, E. G. Mycetomas: An Epidemiological, Etiological, Clinical, Laboratory and Therapeutic Review. *Anais Brasileiros de Dermatologia* [Online] 2018, 93 (1), 8–18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5871356/pdf/abd-93-01-0008.pdf (accessed November 2, 2021) **2. *Data Warrior***. openmolecules. https://openmolecules.org/help/similarity.html (accessed November 2, 2021)