DESIGNING NEW DRUGS BASED ON SNAKE, SCORPION AND MUSHROOM POISONS: SYNTHESIS AND CHARACTERIZATION OF CYSTEINE-RICH MACROCYCLE

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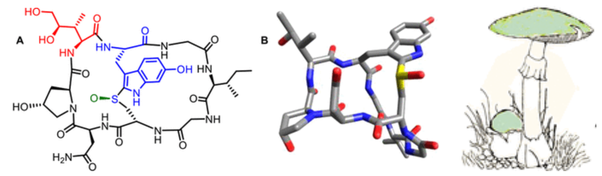
IMPORTANCE OF POISONS

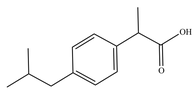


α-Amanitin (shown above) is a natural macrocycle found in the death-cap mushroom and has shown promise as a **potential chemotherapy drug**. In experiments by Kume et al., sub-peritoneal injections of α-amanitin prevented chemotherapy-resistant cancer relapse.

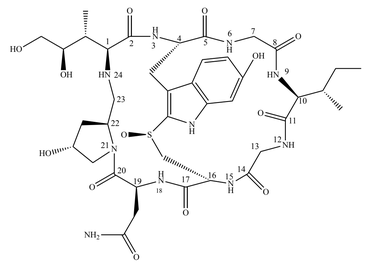
The structure of α-amanitin is heavily informed by its bicyclic structure, which increases rigidity; however, the synthesis of the structure is both long and tedious. In this project, the cysteine-rich macrocycle is produced using a **simple and efficient synthesis** to yield a macrocycle containing the same number of ring atoms as α-amanitin (24 atoms). This synthetic strategy generates the question: can similar, biologically useful molecules be synthesized easily?

Images Adapted From:
Kaveh Matinkhoo, Alla Pryyma, Mihajlo Todorovic, Brian O. Patrick, and David M. Perrin
Journal of the American Chemical Society **2018** *140* (21), 6513-6517

DRUGS FROM PHARMA AND NATURE

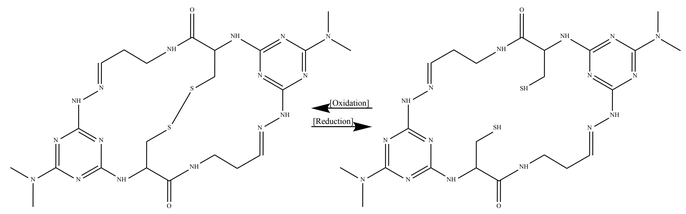


Ibuprofen:
Derived: Pharmaceutical Synthesis
Use: General Pain Relief



α-Amanitin
Derived: Death-Cap Mushroom (*Amanita phalloides*)
Use: Potential Chemotherapy Drug

THIS PROJECT

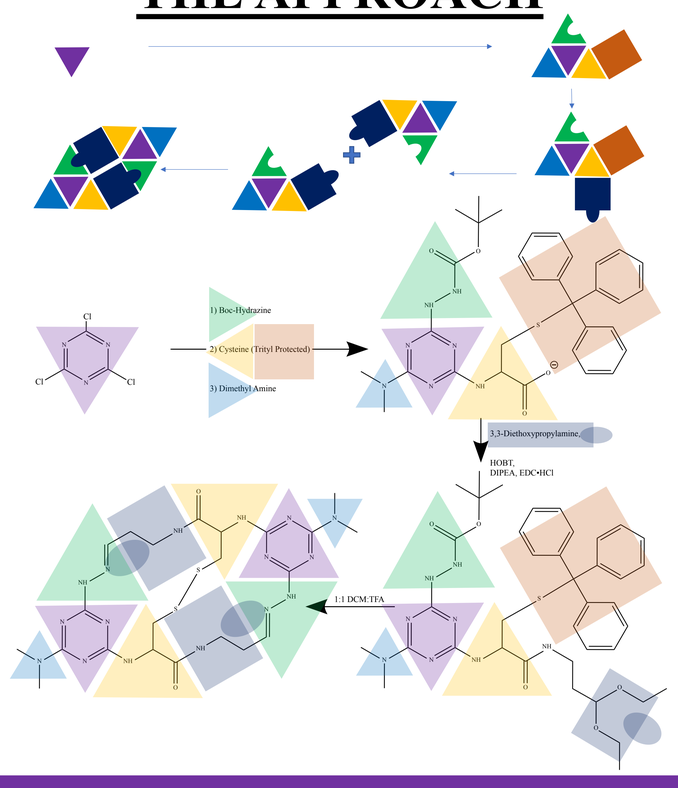


Cysteine-Rich Macrocycle

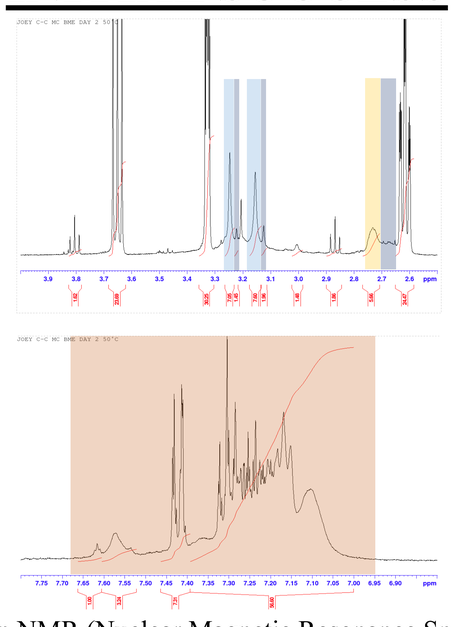
This project aims to synthesize and characterize the cysteine-rich macrocycle shown above, determine the conformation of the molecule in solution, and evaluate the bioactivity of the molecule as a potential drug candidate.

As shown above, the molecule can exist as either the oxidized (disulfide) or reduced (thiol) forms. Because the molecule is more rigid in the disulfide arrangement and less rigid in the thiol arrangement, the importance of rigidity on bioactivity can be tested.

THE APPROACH



INITIAL SUCCESS



Proton NMR (Nuclear Magnetic Resonance Spectroscopy) of Cysteine-Rich Macrocycle

CONCLUSION & FUTURE WORK

1) Cysteine-rich macrocycles have been successfully synthesized using a reproducible and efficient pathway.
2) LogP, variable temperature NMR, H/D exchange, and x-ray crystallography experiments to be run to determine the conformation of the macrocycle in solution
3) Experiments regarding the bioactivity of the molecule are required to determine this molecule's potential use as a novel drug

ACKNOWLEDGMENT

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References:
1. Kume, K.; Ikeda, M.; Miura, S.; Ito, K.; Sato, K. A.; Ohmori, Y.; Endo, F.; Katagiri, H.; Ishida, K.; Ito, C.; Iwaya, T.; Nishizuka, S. S. *Sci. Rep.* **2016**, *6*, 15