Synthesis of Janus Macrocycles

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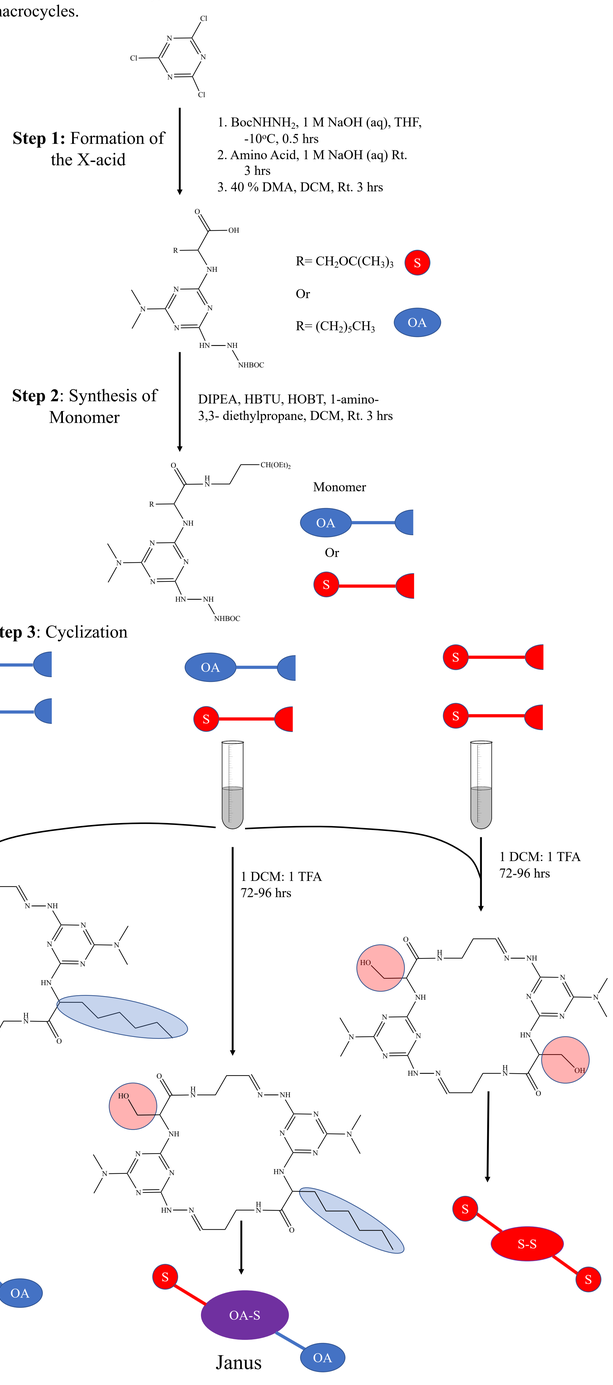
Introduction: One of the most desirable characteristics for a drug is its ability to be taken orally. Drug companies and patients efforts to develop new computational models for predicting logP values for these molecules because the industry standards fail. alike prefer taking a pill over injecting a medicine. Parameters for predicting whether a molecule can be taken orally have been developed. The most common parameter is logP, the log of the ratio of concentrations of drug when added to a mixture of oil and water. Most orally available drugs have logP values between 0 and 4. These values mean that the ratio of drug in oil and water varies from 1-to-1 to 10,000-to-1. Not surprisingly, drugs are reasonably oily (hydrophobic) like the membranes they must cross to access the body. Unfortunately, this requirement also means that hydrophilic groups that could bind tightly to a drug target cannot be included in design. The goal of this research project is to develop strategies to convey drugs with hydrophilic groups across the membrane. This poster describes the synthesis of Janus-molecules with one face being hydrophobic and the other hydrophilic. Understanding the balance of these factors could influence drug design in industry. The molecules themselves are dimers making it possible to synthesize a molecule with two hydrophilic groups **(S-S),** two hydrophobic groups **(OA-OA)** and one of each **(OA-S).** The logP values for these compounds are -6.1 (too hydrophilic), 4.4 (a little to hydrophobic) and 0.8 (within the desired range). This poster details the design, synthesis and characterization of these molecules and describes ongoing research.

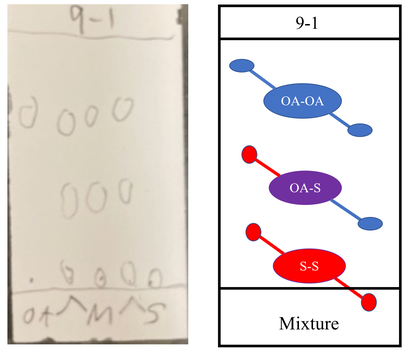
Two Different Monomers Yield Three Different Macrocycles[1]

A step wise process was performed twice to create two different halves of the macrocycle, the monomers. From here three different cyclization reactions were performed. The first was with **OA monomer** to make **OA-OA**. The second was with **S mono**mer to make **S-S**. Lastly, **OA monomer** and **S monomer** were allowed to react to create **OA-OA, S-S** and **OA-S** macrocycles.



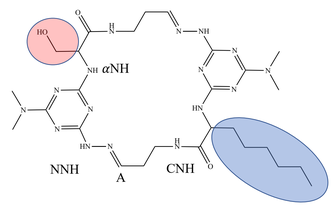
TCL Shows the Presence of Janus Macrocycle in Reaction Mixture

TLC of reaction mixture indicates synthesis of an intermediate, Janus, between the R_f of OA-OA macrocycle and S-S macrocycle.

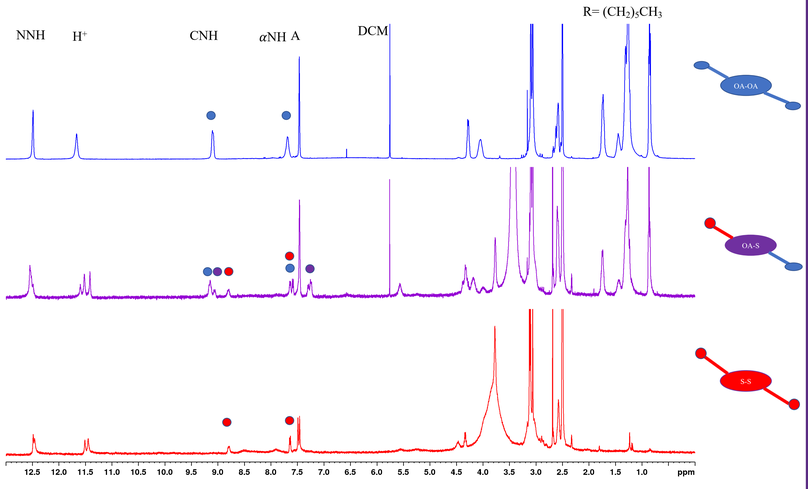


The Fingerprint Region Shows Existence of all Three Macrocycles

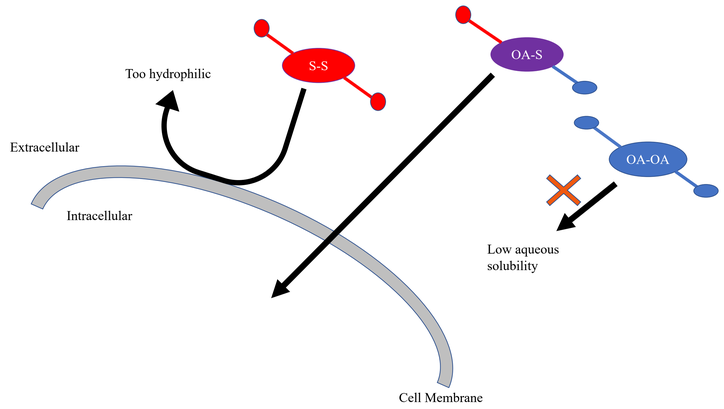
Janus Macrocycle structure with significant protons labeled for NMR identification.



Comparing NMR spectra of **OA-OA** and **S-S** show characteristic peaks that can indicate the presence of Janus



Janus Provides an Intermediate Between Two Extremes to Potentially Partition Though Membrane



HPLC Provides a Value for Janus that is in Between OA-OA and S-S Macrocycle

HPLC results of the reaction mixture shows that the hydrophobic characteristic of OA allows for a measurable log P of a macrocycle containing a hydrophilic group.

Macrocycle	Log P
OA-OA	4.2
OA-S	0.8
S-S	<<-2.2

Conclusions

- Three macrocycles were synthesized with unique chemical characteristics.
- Synthesis of Janus macrocycle creates an intermediate product that contains a logP between the to homodimers

What is Next!

- Synthesizing other heterodimers with is see if a statical equation can be created to predict the heterodimer logP.
- Work on isolating Janus to further prove synthesis.

Reference

1. Alexander J. Menke, Camryn J. Gloor, Liam E. Claton, Magy A. Mekhail, Hongjun Pan, Mikaela D. Stewart, Kayla N. Green, Joseph H. Reibenspies, Giovanni M. Pavan, Riccardo Capelli, and Eric E. Simanek *The Journal of Organic Chemistry* **2023** *88* (5), 2692-2702 DOI: 10.1021/acs.joc.2c01984

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