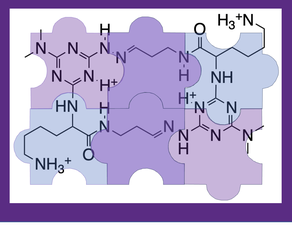

Models for the Next Generation of Drugs

Design, Synthesis, and Conformational Analysis of a 26- Atom Macrocycle

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To fight disease, pharmaceutical companies have historically prepared small molecules designed to interfere with specific sites on proteins (enzymes) to prevent chemical reactions from taking place. However, a second paradigm for interfering with proteins has gone largely unexplored--blocking protein-protein interactions. To accomplish the latter, large molecules are needed to bind to large areas on the protein target. However, large molecules present additional challenges. Typically, they are hard to synthesize, not orally available, and cannot cross cell membranes. Nature has designed large molecules like cyclosporin that should not work as drugs based on our current understanding. Despite its size, cyclosporin is orally available and can cross cell membranes. This research explores the design, synthesis, and conformational analysis of similar large ring-shaped molecules, so-called macrocycles. In this work, we are increasing the size of the ring-shaped molecule. By increasing the size of the ring-shaped molecule and varying the amino acid (in this case, valine), we are expanding the possible ways in which our macrocycle may interfere with protein-protein interactions. Here, a 26-atom macrocycle is reported. ^{1}H NMR spectroscopy reveals a protonated molecule that is highly dynamic which has access to a beta-sheet conformation.

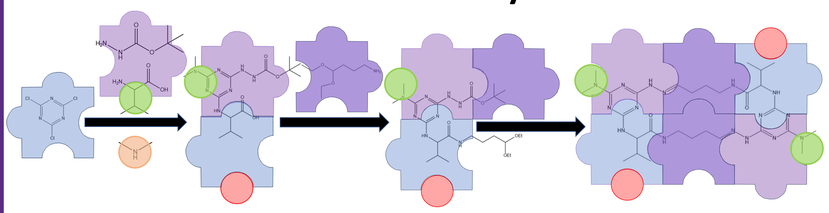
Brief Overview of Our Group

Who: Our group consist of seven undergraduate Chemistry, Biology, and Biochemistry majors and four Chemistry PhD students led by Dr. Eric Simanek.

What: The main focus of our group over the past five years has been the synthesis and characterization of triazine macrocycles.

Why: These triazine macrocycles are significant for four reasons. First, they can be customized in a variety of ways (size, hydrophilicity, etc). Second, the cyclization event is quantitative which results in relatively high yield, something quite rare in the world of macrocycle synthesis. Third, many of our group's macrocycles have shown to exhibit biologically relevant logPs. By far the most important reason, though, is there proposed mechanism of action. Many diseases are not treatable via traditional small drugs. These macrocycles aim to interfere with maladaptive processes such as improper intracellular signaling and protein aggregation.

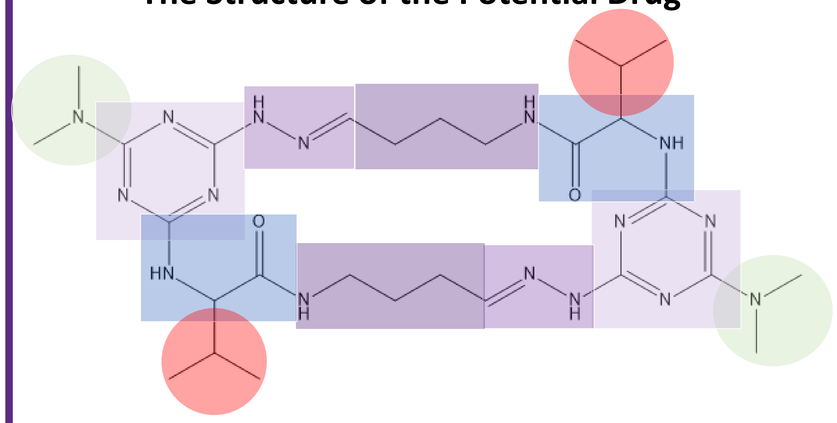
How this Molecule is Synthesized



Big Ideas:

- Start with relatively cheap starting materials to limit cost of production
- Incorporate methods that limit overall reaction time
- Use reactions that have high yields to increase cost effectiveness

The Structure of the Potential Drug



Though different molecules have been used in the past, DMA has proved to provide the greatest reactivity and clearest ^{1}H NMR imaging.

[s]-Triazine is the centerpiece of the molecule. It provides a reactive centerpiece for our substrate molecules to snap into via S_NAr.

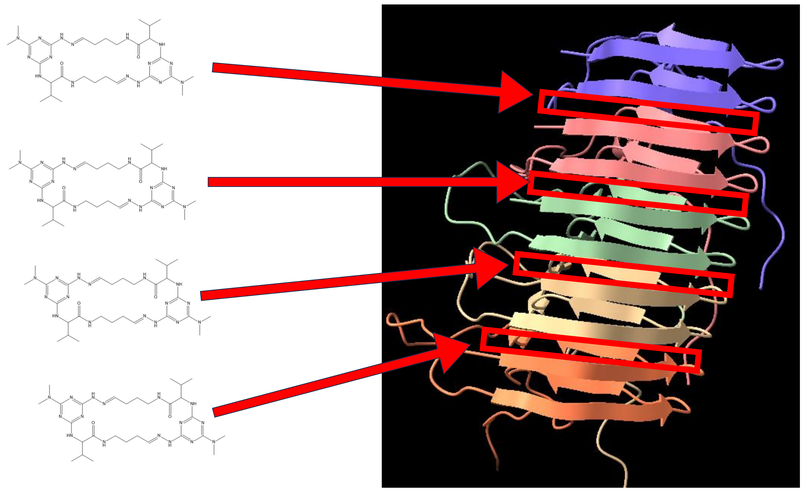
This hydrazine derivative forms a double bond to the molecule, providing a site for hydrogen bonding within the macrocycle as well as providing a highly reactive site for macrocyclization.

This section of carbons comes from the 4,4-diethoxybutyl-1-amine group, which serve to elongate the size of the ring. Compared to our more studied molecules in the group, this compound has a longer carbon chain which alters its form.

The carbonyl from the amino acid participates in hydrogen bonding with the interior nitrogen of the triazine and sp^2 nitrogen of the hydrazine in other molecules. While it is yet to be proven, we suspect that a similar process could occur in this molecule.

As mentioned in the next section, the R group is a site of variation within our group synthesizing 26 member macrocycles.

Long Term Goal



Example schematic of how our macrocycle would interact with Beta – Amyloid aggregation

Protein-protein aggregation can promote dysfunction within organ systems. This behavior is the cause of prevalent diseases such as Alzheimer's and Lewy Body diseases.

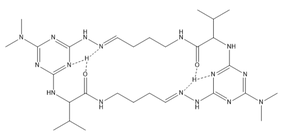
Our molecule is designed to mimic beta-sheet structure. Our goal is to design a molecule that could enter areas where these diseases occur and prevent the aggregation of these proteins.

Today our goal is to continue to create a library of molecules to understand their behavior and determine their suitability as drugs.

Conclusions

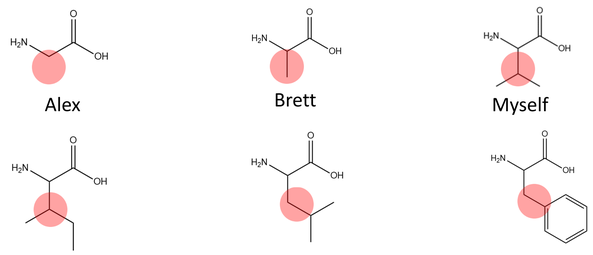
- It is possible to synthesize these molecules.
- This molecule can be synthesized with high yields.
- Further analysis and documentation will be needed to confirm the structure, hydrophilicity, and other traits of the molecule.

Proposed Hydrogen Bonding Pattern



Assuming preliminary data is confirmed, this is the hydrogen bonding structure our molecule would obtain under acidic conditions. This structure would likely have increased rigidity and stability, but this is yet to be confirmed

Our Focus: Exploring Variance in Functionality from Changes in Structure



The six members of our group have created slightly different molecules from one another. By using different essential amino acids, we evoke changes in the properties of the overall molecule.

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