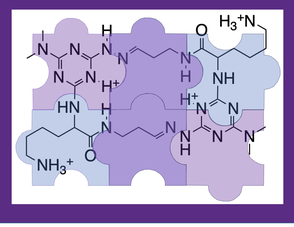

Reimagined Route to Drug Discovery: Macrocyclization leads to 20 predicted and persistent products for chemical library development

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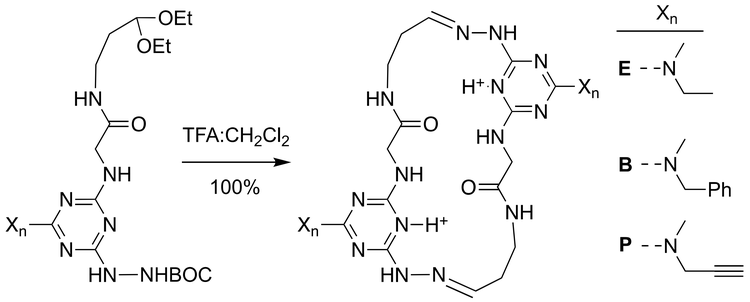
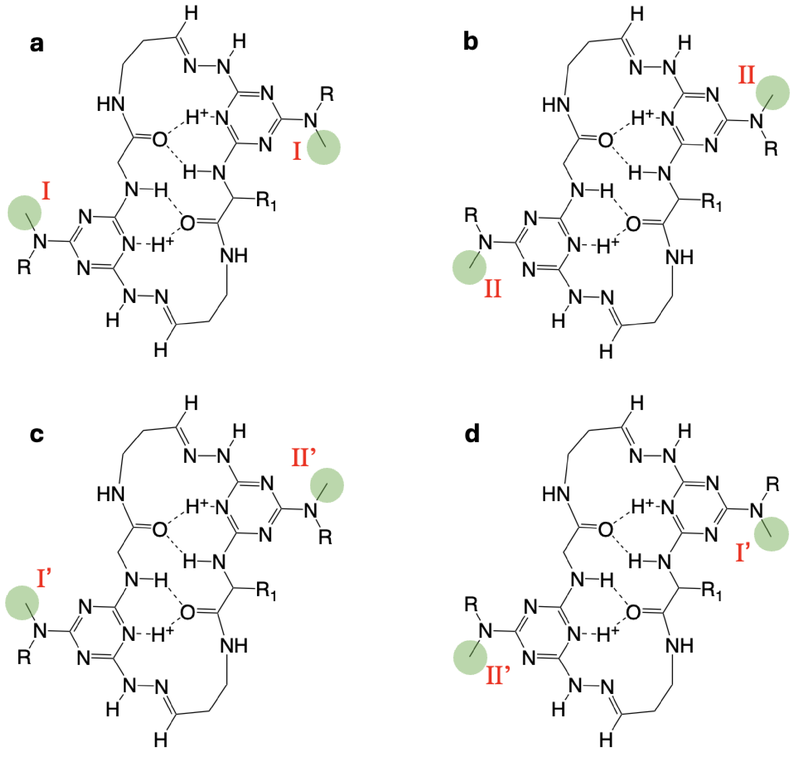
ABSTRACT: In the pursuit of new ways to develop libraries of compounds for pharmaceutical drug discovery, the utilization of a robust and tunable macrocycle synthetic scaffold has led to the discovery of persistent and structurally well-defined conformational isomers. Targeting these macrocycles that exist as an ensemble of preorganized conformations represents a compromise between the pursuit of flexible molecules of undefined structure and rigid molecules biased towards a single conformation. This system is based on the quantitative dimerization of a monomer to afford macrocycle. When a single monomer is used, six unique structures are obtained. When two monomers are used, twenty unique structures are obtained. These different structures (conformational isomers) are accessed via hindered bond rotation with a barrier of ~18 kcal/mol and are observable by ^{1}H NMR. Current drug discovery methods heavily rely on screening large chemical libraries of small, ridged molecules against protein targets and typically sacrifice entropy in favor of stronger ligand-target binding. Using our system, synthesis of 50 monomers allows for the generation of a library of over 10,000 structurally unique macrocycles. The goal of this work is to provide new chemical libraries for drug discovery.

Macrocycles are cyclized with different asymmetric secondary amines

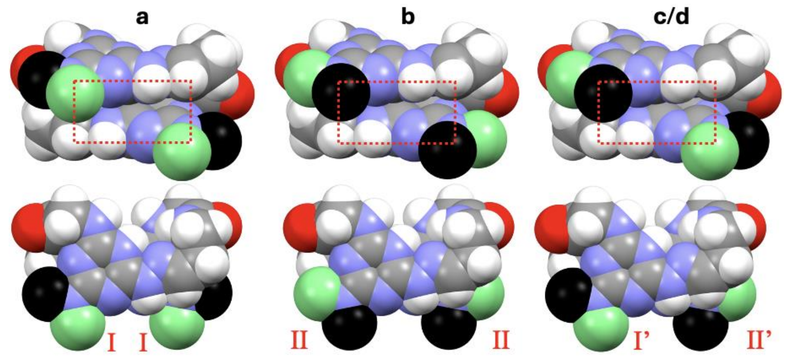


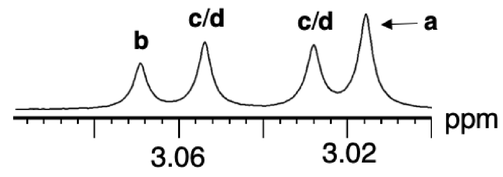
There are **four** different conformational isomers which can be generated using asymmetric secondary amines



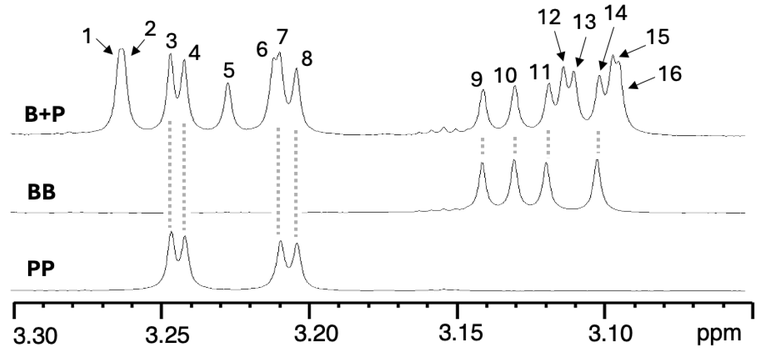
Isomers c and d are degenerate leading to **three** different possible structures (6 using chiral amino acids)

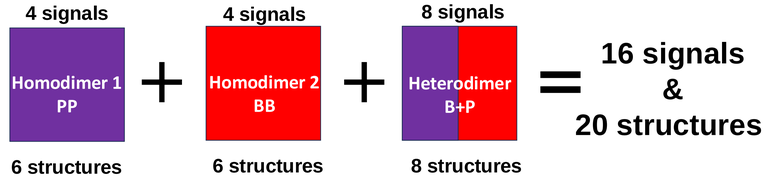
Methyl group acts as reporter for the **three** different environments of homodimers



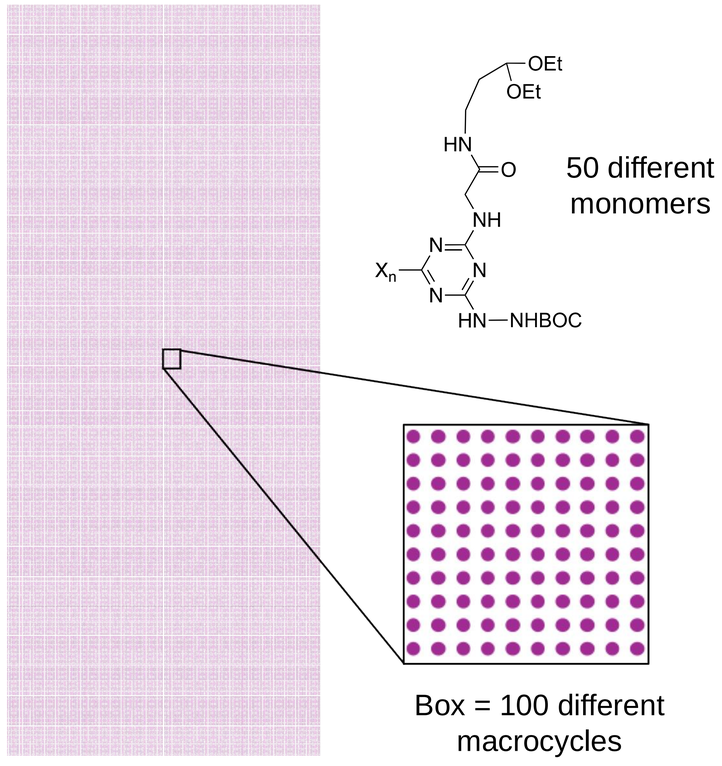


Using two different monomers to make heterodimer allows us to access to **twenty** unique structures





50 different monomers can quickly lead to over 10,000 macrocycles



Conclusions using asymmetric amines

- Making homodimer can lead to 6 different unique macrocycle structures
- Making heterodimer can lead to 20 different unique macrocycle structures
- Making 50 different monomers leads to over 10,000 different structures for library synthesis

Startup Company Coming Next…

Liam Claton – is a third-year graduate student on track to graduate next year who has been working to take this work and build a startup company developing innovative chemical libraries of macrocycles for pharmaceutical companies and academic research groups in the pursuit of new medicines.

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