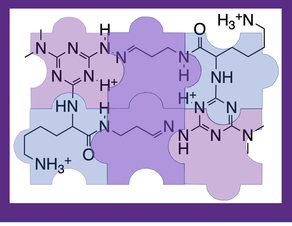

New Approaches to Macrocycle Synthesis

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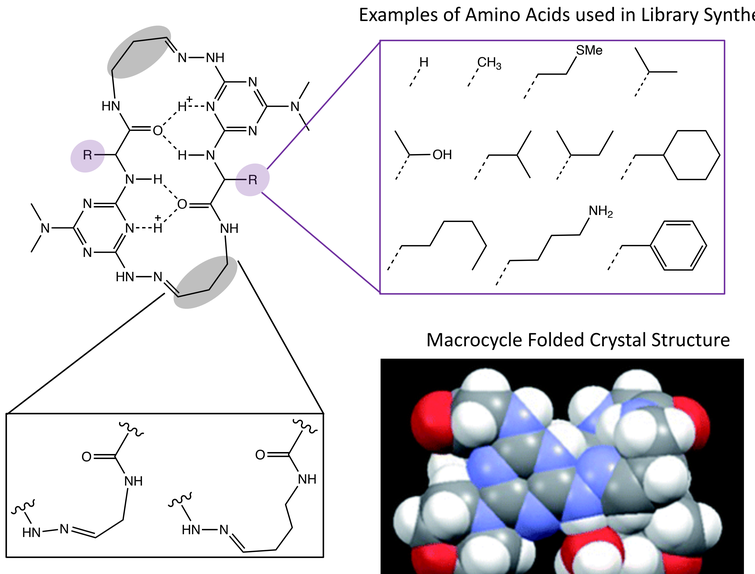
ABSTRACT: Creating a diverse array of structurally distinct, triazine-containing, macrocycles remain the focus of the Simanek group. Until now, this goal has been accomplished through a straightforward 3 step synthetic route with variation of amino acid incorporation and acetal length. Currently two new approaches to macrocycle synthesis are being pursued. The first approach relies on two like monomers coming together: by changing the relative position of groups in the macrocycle, the persistence of shape can be probed. The second approach relies on two different monomers coming together. Using a similar synthetic route, this strategy, if successful, will allow much finer control over design and engineering these molecules for specific purposes. These libraries of structurally diverse macrocycles are important for the long-term goals of establishing rules that can guide pharmaceutical drug design in these under-explored types of molecules.

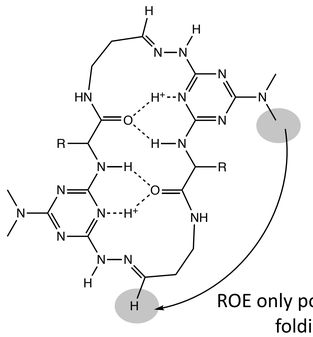
The Simanek group has synthesized a diverse library of triazine containing macrocycles



Macrocycle Folded Crystal Structure

Unique properties of macrocycles emerge based on variation in 3D conformation

Dynamic folding motion

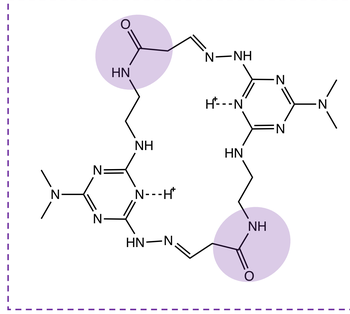


Pharmaceutically Relevant Range of LogD Values

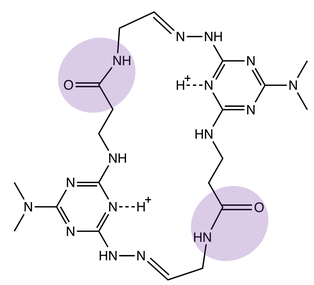
Amino Acid	LogD
Glycine	-3.6
Alanine	-1.9
Tyrosine	-1.7
O-Actyl-Tyrosine	-0.3
Methionine	0.1
Valine	0.4
Isoleucine	1.4
Phenylalanine	1.4
Leucine	1.6
Cyclohexylalanine	4.1
Octanoic Acid	4.1

New Approach 1: Changing the relative position of the amide

New target with inverted amide

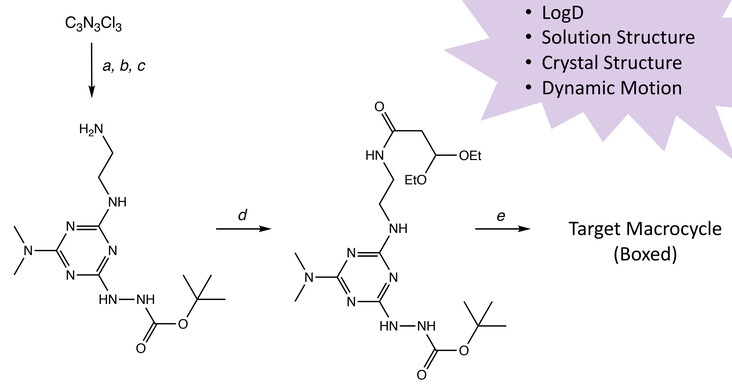


Previously Synthesized β-Alanine Macrocycle



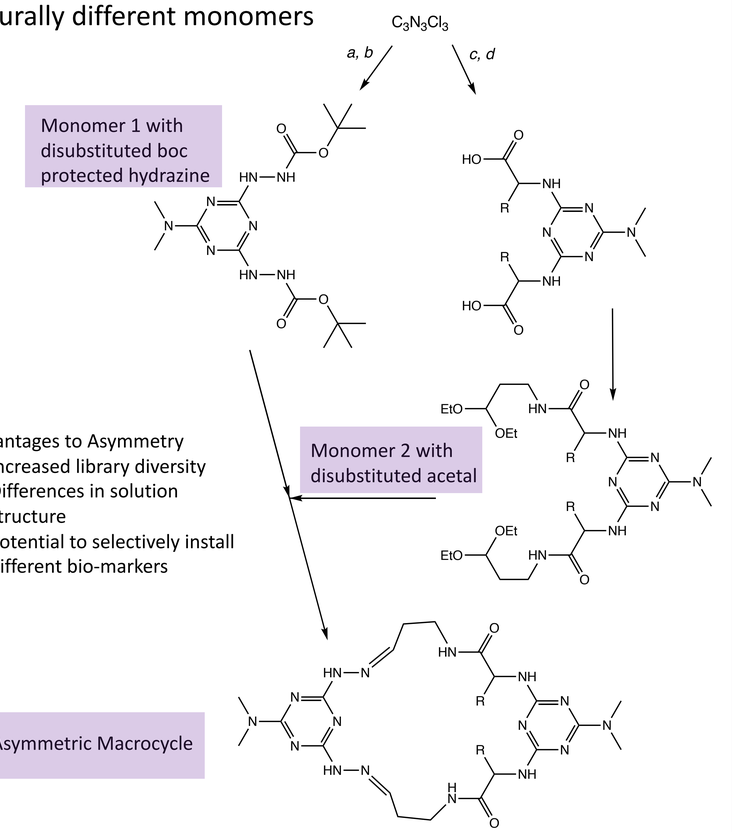
Planned Comparisons
- LogD
- Solution Structure
- Crystal Structure
- Dynamic Motion

Synthetic Approach



Synthesis of New Approach 1. a) BOC-hydrazine, 0 °C, NaOH*(aq)*; b) ethylene-diamine, RT to 50 °C; c) CH_3NHCH_3; d) 3-3 diethoxypropanoic acid, HBTU, HOBT, RT; e) 1 : 1 TFA : CH_2Cl_2.

New Approach 2: Asymmetric macrocycle achieved by two structurally different monomers



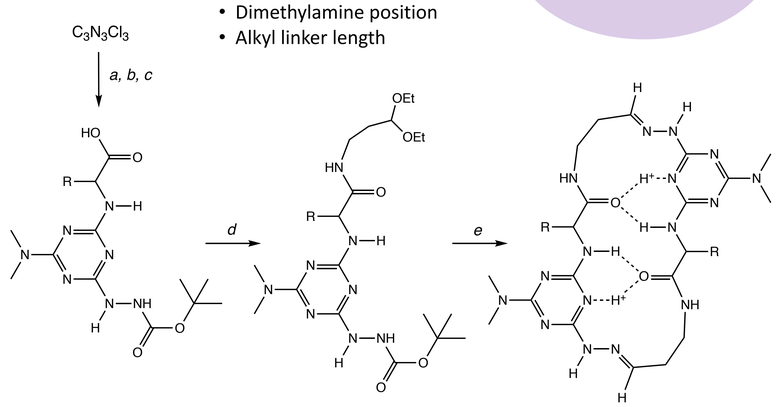
Advantages to Asymmetry
- Increased library diversity
- Differences in solution structure
- Potential to selectively install different bio-markers

Synthesis of New Approach 2. a) BOC-hydrazine, 0 °C, NaOH*(aq)*; b) CH_3NHCH_3; c) amino acid , RT, 50 °C; d) CH_3NHCH_3; e) 3-amino-1,1-diethoxypropane, HBTU, HOBT, RT; f) 1 : 1 TFA : CH_2Cl_2.

Previous 3-Step Synthetic Route to Macrocycle

Advantages
- Quantitative cyclization yield
- 3 potential areas for structural variation
  - Amino acid
  - Dimethylamine position
  - Alkyl linker length

How can we modify this synthesis to access new macrocycle structures?



Synthesis of the macrocycles. a) BOC-hydrazine, 0 °C, NaOH*(aq)*; b) amino acid, RT to 50 °C; c) CH_3NHCH_3; d) 3-amino-1,1-diethoxypropane, HBTU, HOBT, RT; e) 1 : 1 TFA : CH_2Cl_2.

Conclusions

- By expanding the synthetic approaches to triazine containing macrocycles we can expand their chemical characteristics and potential applications
- Further work is needed to optimize the synthesis and characteristics of these macrocycles

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References:

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