Furthering Control of Drug Design; N-Alkylated Triazine Macrocycles Display Unique Conformations

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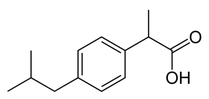
Oral Drug Design Philosophy

For pharmaceuticals to be able to be taken by mouth, they need to be "orally available" and be soluble in both aqueous (blood) and organic (lipids) media.

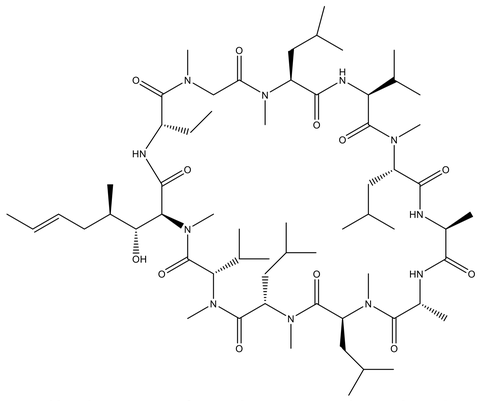
Lipinski's "rule of five" describes the parameters for good solubility in both aqueous and organic media:

- *No more than 5 hydrogen bond donors*
- No more than 10 hydrogen bond acceptors
- A molecular mass less than 500 daltons
- An octanol-water partition coefficient (log *P*) that does not exceed 5



Ibuprofen

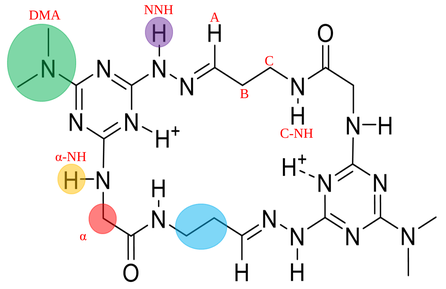
N-Alkylation, Macrocycles, and Cheating the Rule of Five



Cyclosporin

N-Alkylation (replacing the hydrogen of the amine of an amino acid) is a useful tool to lower the number of hydrogen bond donors. Macrocycles can adopt multiple conformations to be more soluble in aqueous or organic media, therefore not needing to strictly follow the rule of five.

N-Alkylated Amino Acids Macrocycles

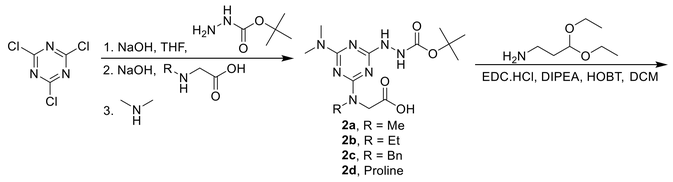


Various previously modified positions:
- Different amine
- α-substitution
- Different acetal chain lengths
- NNH-substitution

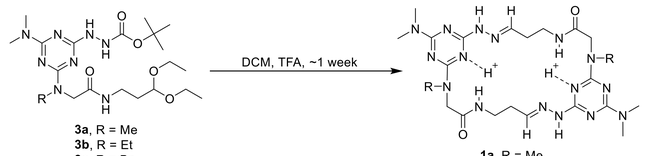
α-NH/R has yet to be tested before this paper

Our group has previously used naturally occurring amino acids for the macrocycles. This project tests the structure of *N*-alkylated amino acid macrocycles compared to a reference glycine macrocycle.

Synthetic Scheme



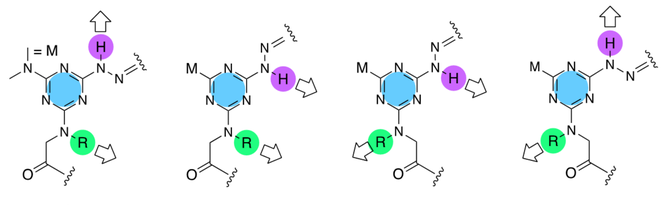
2a, R = Me
2b, R = Et
2c, R = Bn
2d, Proline



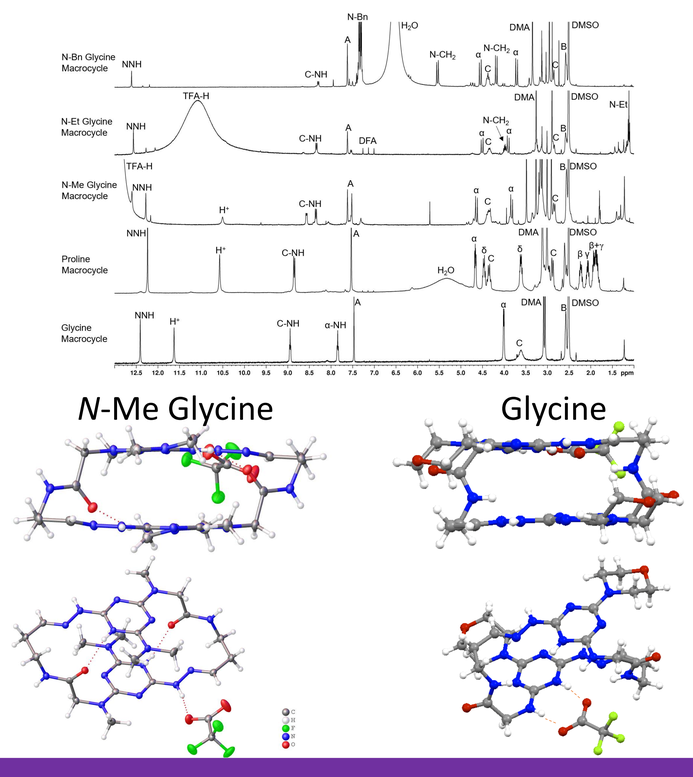
3a, R = Me
3b, R = Et
3c, R = Bn
3d, Proline

1a, R = Me
1b, R = Et
1c, R = Bn
1d, Proline

Possible Rotamer Structures



N-Alkylation Leads to New Structures



N-Me Glycine

Glycine

Conclusion and Future Work

N-Alkylation of our macrocycles leads to novel structures and control of their dynamics through more rigid configurations.

Future Work:

- Acquire crystal structure data of other macrocycles to compare solution and solid state
- Find the log*P* value for each macrocycle

Acknowledgement

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