Implications of Steric Congestion on Sheet Formation: 26-Atom Macrocycles

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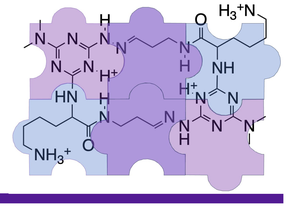
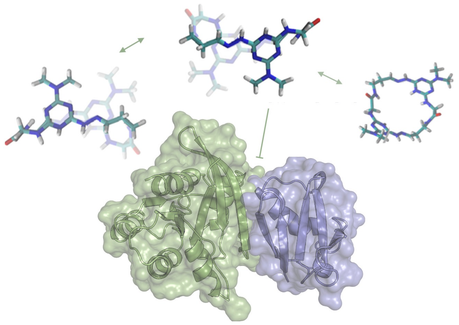


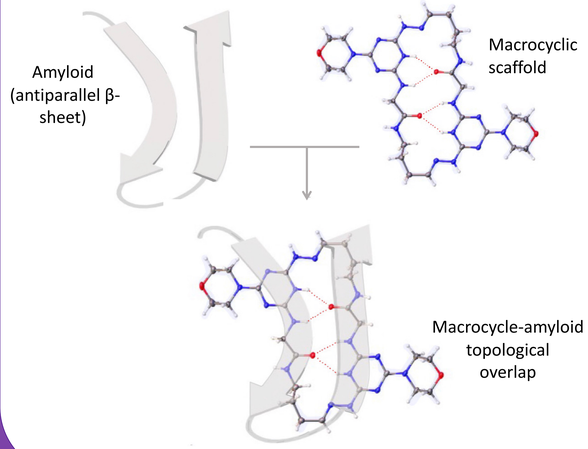
NEW AVENUE FOR DRUG DESIGN

Macrocyclic drugs adopt multiple conformations—a behavior referred to as chameleonicity—to navigate hydrophobic cellular membranes and aqueous intracellular environments. These molecules can be explored as a modality for inhibition of protein-protein interactions due to the range of structural modifications they can tolerate.

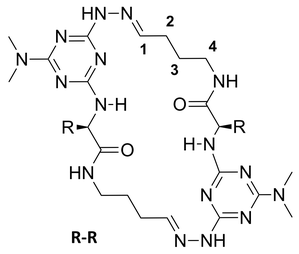


MOLECULAR ENGINEERING OF MACROCYCLES

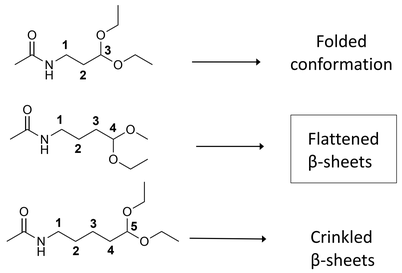
Molecular engineering of macrocyclic compounds can present avenues to potentially halt Alzheimer's disease pathways. Alzheimer's involves the aggregation of amyloid peptides that exhibit ***β-sheet structures.*** Thus, designing macrocycles that structurally/topologically mimic ***β-sheets*** should enhance the affinity of these macrocycles towards the amyloid aggregates, preventing amyloid plaque formation.



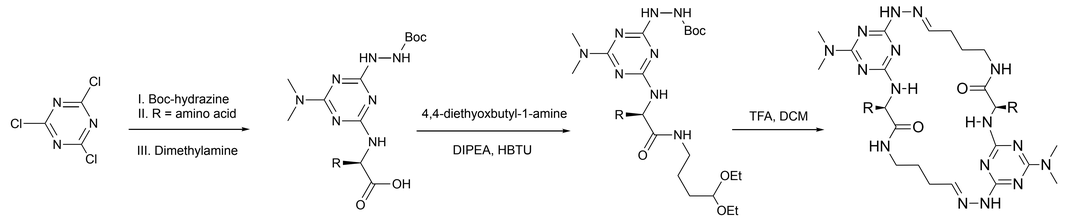
PROPOSED SCAFFOLD SUPPORTS β-SHEET STRUCTURE



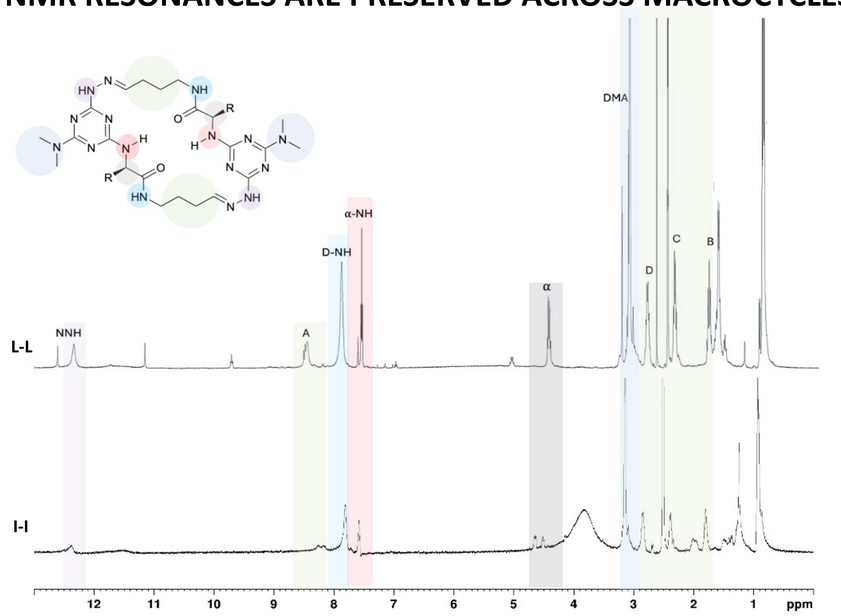
We **propose** a 26-Atom scaffold as a β-sheet mimic and potential inhibitor of amyloid fibril aggregation. X-ray crystallography has proved acetal length dictates morphology. Incorporating a 4-carbon long acetal group should give rise to a flat, extended conformation reminiscent of a ***β-sheet.***



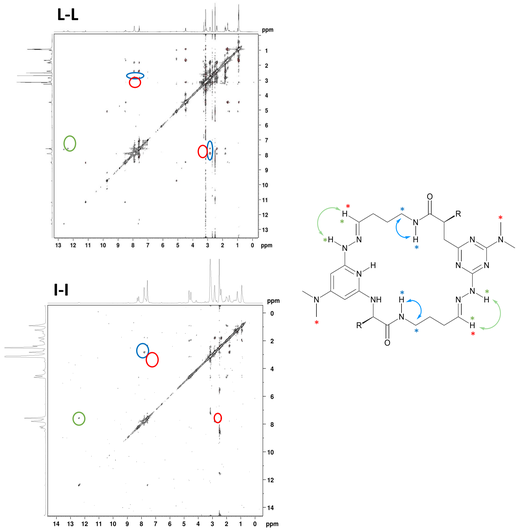
QUANTITATIVE CYCLIZATION IN THREE STEPS



^{1}H NMR RESONANCES ARE PRESERVED ACROSS MACROCYCLES



2D-NMR TECHNIQUES PROBE SOLUTION STRUCTURE



CONCLUSIONS & FUTURE WORK

- Manipulating the acetal length is important for carefully control the topological arrangement (i.e., folded vs unfolded) of the target macrocycle.
- Different amino acids and auxiliary groups can be incorporated to confirm that 26-atom ring sizes maintain an unfolded conformation in solution.

REFERENCES

1. Sharma, V. R.; Mehmood, A.; Janesko, B. G.; Simanek, E. E. Efficient Syntheses of Macrocycles Ranging from 22-28 Atoms through Spontaneous Dimerization to Yield Bis-Hydrazones. *RSC Adv.* **2020**, *10* (6), 3217-3220. https://doi.org/10.1039/c9ra08056b

ACKNOWLEDGMENTS

We thank the Robert A. Welch Foundation, the NIH and the TCU Science and Engineering Research Center (SERC) for their financial support.