Exploring molecular design: A chemical library reveals a surprisingly hydrophobic diamine

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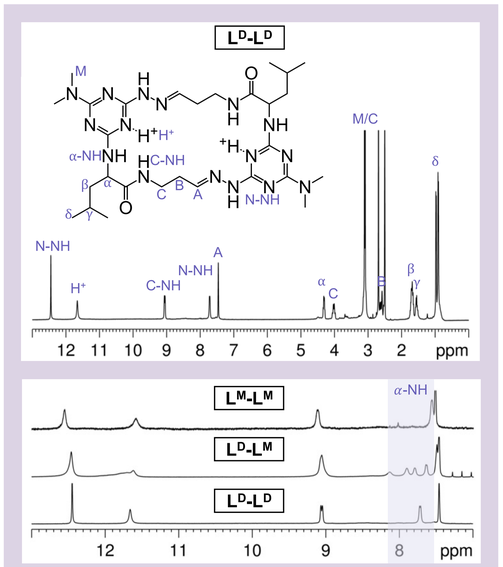
Introduction

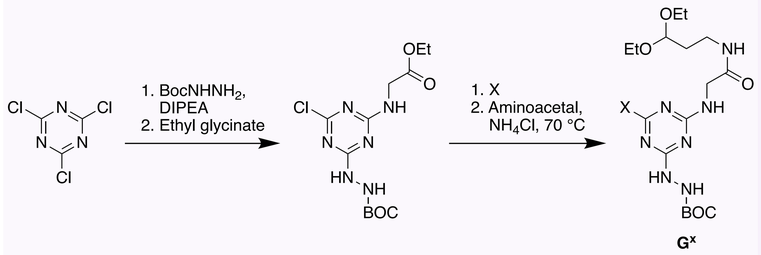
Macrocycles offer therapeutic potential but remain poorly understood, largely due to synthetic challenges and unpredictable solubility. We address these challenges by synthesizing a library of 24-atom macrocycles to investigate structure-partition coefficient relationships. Six auxiliary amines and two amino acids produced 11 monomers, which quantitatively dimerize upon acid treatment to generate 36 distinct macrocycles. Measured octanol:water partition coefficients (logP) span a wide range of values (-0.3 to 5.2). Substitution effects were compensatory, and one macrocycle containing a diamine was surprisingly hydrophobic. Structural analysis and computation provide a rationale for these observations.

NMR Confirms Synthesis

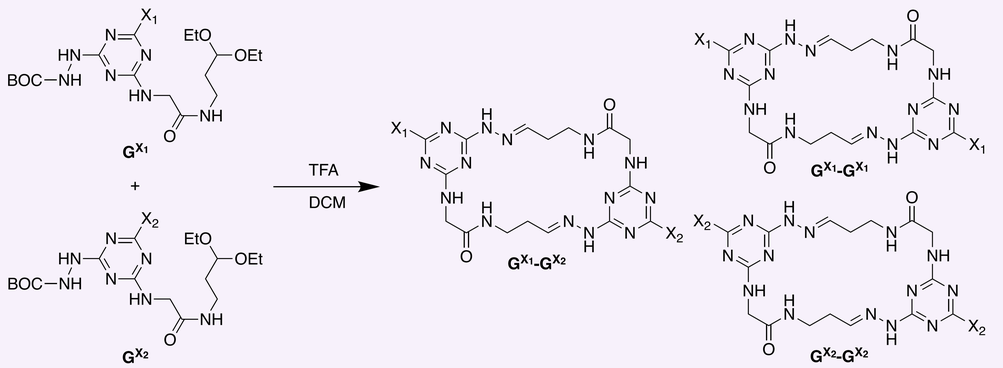


Synthetic Route to a 36-Member Library of Macrocycles

Six distinct glycine-based monomers and five leucine-based monomers were obtained by incorporating different auxiliary amines, X. The scheme employed for monomers containing glycine is shown below.

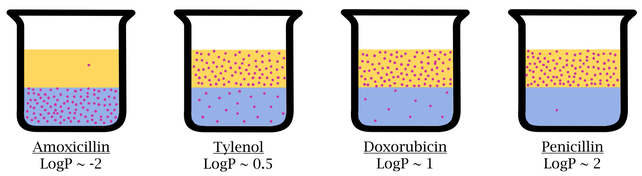


Equimolar portions of two monomers quantitatively dimerize upon acid treatment to yield macrocycles in a 1:2:1 ratio of homodimer (X_1–X_1) : heterodimer (X_1–X_2) : homodimer (X_2–X_2). The five leucine-derived monomers formed 15 distinct macrocycles. Similarly, six glycine-derived monomers produced 21 macrocycles, following the formula $\frac{n(n+1)}{2}$ for n, monomers.

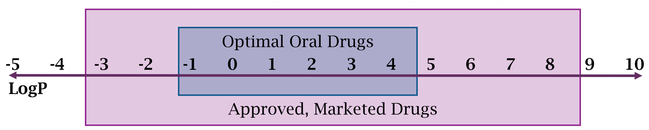


LogP and Oral Availability

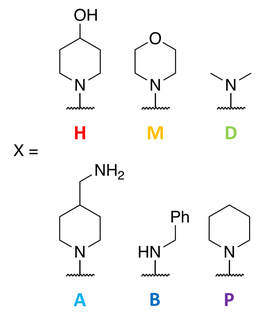
LogP quantifies how a molecule partitions between oil and water and has implications for drug absorption.

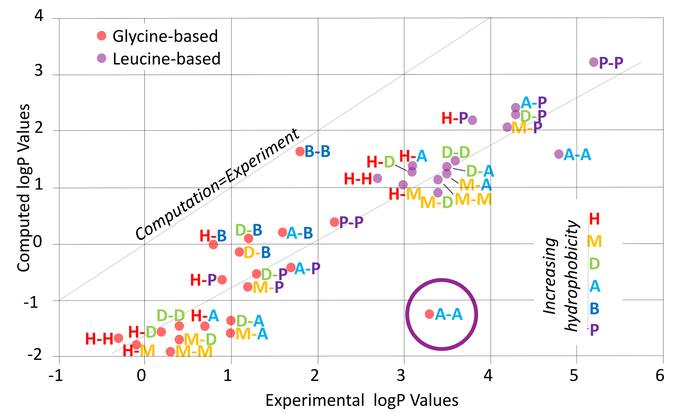


Optimal oral absorption occurs around a LogP of 1.5, while drugs with LogP values outside the optimal range often must be given via injection.

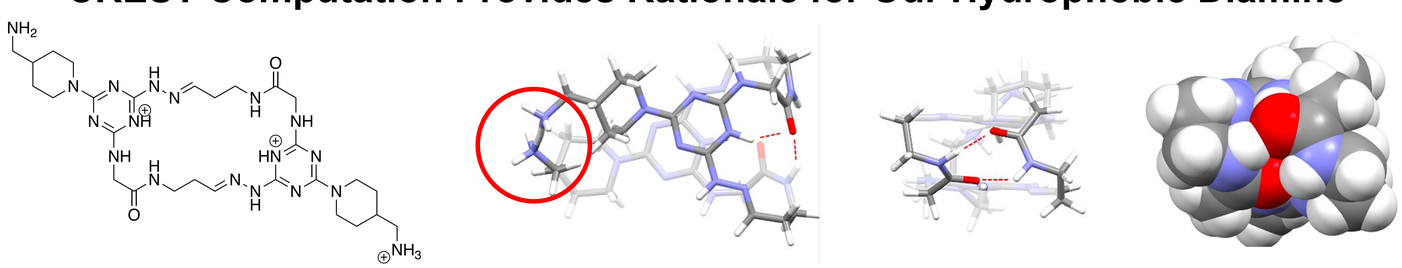


Amine Variation Leads to a Broad Range of LogP Values





CREST Computation Provides Rationale for Our Hydrophobic Diamine



References

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Acknowledgements

We thank the Robert A. Welch Foundation (P-0008) and the NIH (R15GM135900) for support.

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