Activity-Structure Relationship: How logP Values of Triazine Macrocycles Reflect Different Conformational Groups and Yield Predictive Partition Values

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ABSTRACT: Peptidomimetic macrocycles are of ever-growing interest to the field of pharmacology as candidates for inhibiting supposed "undruggable" sites (such as protein-protein interactions). An important property of pharmacophores within drug development is the partition coefficient (often expressed as logP or logD), which measures the ability of a molecule to partition between aqueous and organic media, effectively expressing the ability for a drug to diffuse into a cell from the bloodstream. Our group has previously synthesized several amino acid-containing triazine macrocycles through facile three-step procedure yielding folded, sometimes dynamic, macrocycles in good yields. With nine additional macrocycles, a trend in logD values has emerged, allowing for the rapid prediction of the macrocyclic conformation per its respective logD values. Each macrocycle is folded, but the extent of triazine-triazine overlap, side chain van der Waals interactions, and shielding of its central proton is reflected in the divergence of the macrocycle's logD from a central trendline. The ability to predict the macrocycle's logD values via additive, atomistic, algorithms is also shown to reveal this divergent trend. Structures of these triazine macrocycles were elucidated through proton and nOesy/rOesy NMR.

Rule of Five as Standard for Predicting Oral Availability of Drugs

Ideal[1,2]

- No larger than 500 Da
- No more than 5 H-Bond Donors
- No more than 10 H-Bond Acceptors
- logP between -0.4 and +5.6
- Polar surface area no greater than 140 Å²

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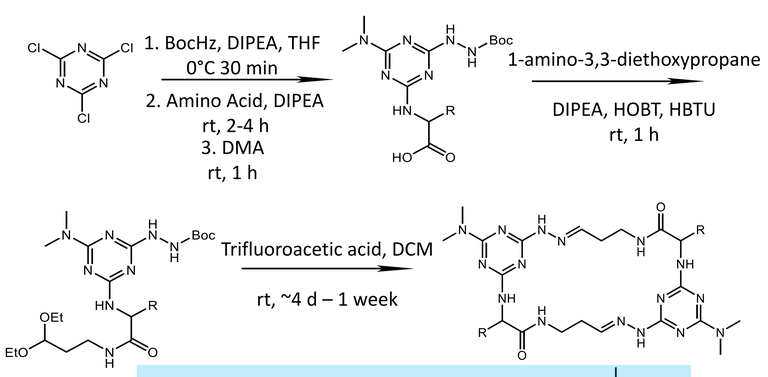
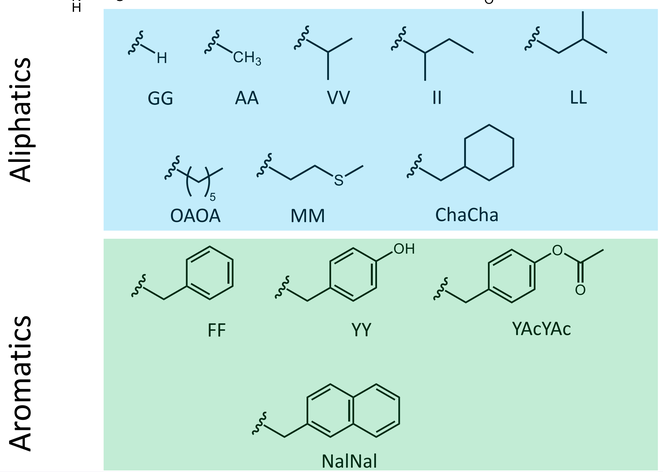
Our Macrocycles

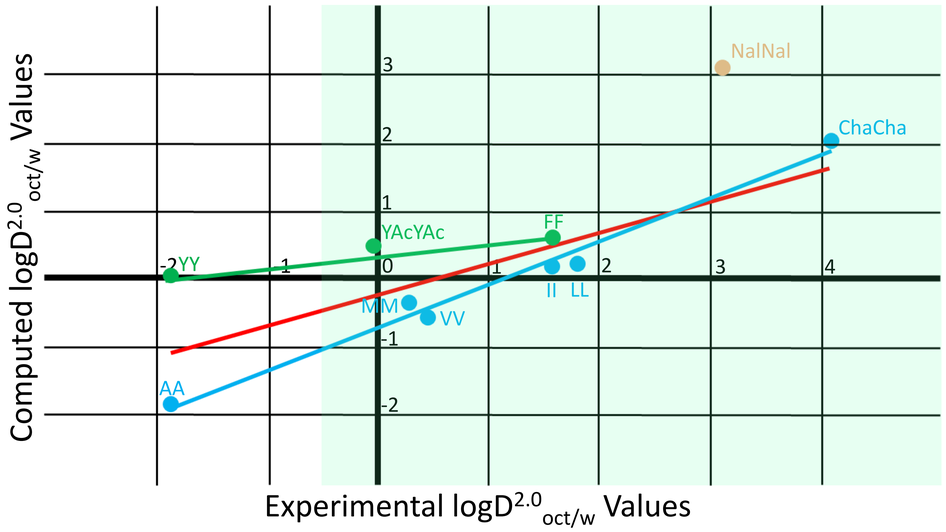
- Smallest is 528 Da
- 6 H-Bond Donors
- 18 H-Bond Acceptors
- logD Values between* -2.2 and 4.2
- Minimum PSA 233.4 Å²

Synthesis of Aliphatic and Aromatic Macrocycles to Test Emergent Conformational Groups

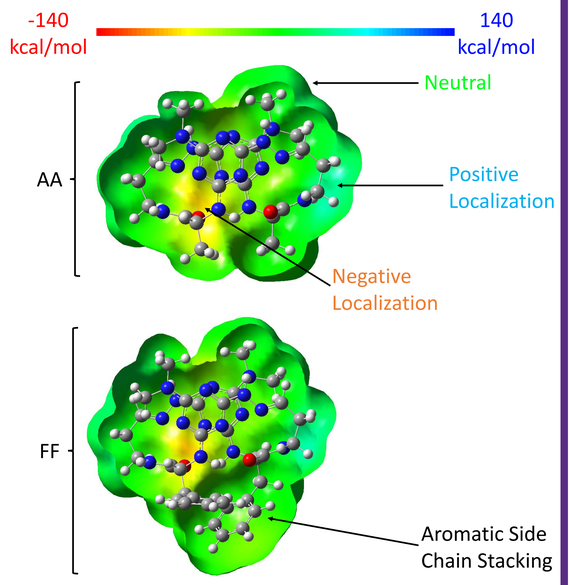




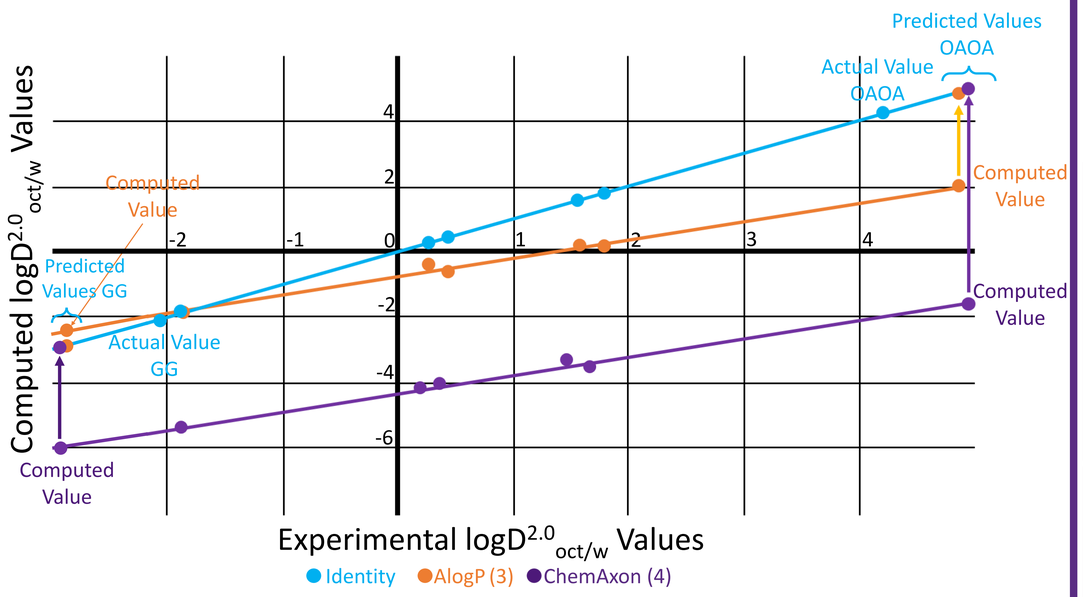
Correlation of Computed and Experimental Values Reveals Distinct logP Trends by Sidechain Identity



Disparate Localization of Charge Benefits Membrane Partitioning



Correction of Computed logP Values Through Experimental Linear Trendline Fitting



Conclusions

- Varying side groups lead to different conformations, including aromatics, aliphatics, and potential Naphtyl-like
- logP trends most likely stem from varying extents of sidechain-sidechain interactions
- Acceptable logP values are permitted for most of our macrocycles despite breaking much of the Ro5
- Additive, atomistic, logP algorithms can be corrected for a model system, leading to useful candidate predictions

Future Work

- Measure cell permeability *via* PAMPA assay
- Expand conformational groups by measuring the logP values of other functional groups (e.g. glutamine, lysine, threonine, etc.) to develop a more comprehensive library
- Compare logP, PSA, total surface area, and other pharmacologically relevant parameters to future *in vitro* docking test
- Explore rationale of divergent trends between aliphatics and aromatics

References:

1) *Adv. Drug. Deliv. Rev.* **2001**, *46* (1-3), 3-26
2) *ACS Comb. Sci.* **1999**, *1* (1), 55-68
3) **2010**. "RDKit." Q2. https://www.rdkit.org/.
4) Marvin JS 22.11.0, **2022**, ChemAxon, http://www.chemaxon.com
5) PSA's computed through: *J. Comput. Chem*. **2012**, *33*, 580-592
6) PSA's visualized through: Gaussian 16, Revision C.01

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