Peptoid Design
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Abstract
Peptoids, synthetic peptide mimics, have shown potential as biological tools and therapeutics. The 3-D structure of peptoids will determine the function of biological activity. Our goal is to discover the factors that will promote helicity in peptoids, and design peptoids that will have the potential to mimic the protein REST (Repressor Element 1 Silencing Transcription Factor).

What is a Peptoid?
A peptoid is a synthetic peptide mimic:
- Side chains used in this study:
  - Charged: Nssb, Nspe, NLeu
  - Aromatic: NLeu, NLys
  - Aliphatic: NGlu

Peptoids lose backbone chirality, which means that the structural determinants will be different from that of alpha peptides.

Peptoids can mimic lung surfactant proteins and antimicrobials.

Advantages of Peptoids vs. Peptides:
- Ability to mimic proteins with increased biostability
- Synthesis is efficient, inexpensive, and easily diversified

REST - A Transcriptional Repressor
REST binds to another protein complex, mSin3, with an amphiphatic alpha helix binding domain.

This data represents qualitative analysis of each peptoid.

Role of Chirality in Promoting Helicity

- CH1, 66% aliphatic chiral, was consistently helical
- CH5, which replaced position 4 NLys with NGlu on CH4, displayed improved helicity
- CH2-CH4 showed some aromatic stacking between i, i+3 residues

Role of Aromaticity in Promoting Helicity

- AR2 showed aromatic stacking between i, i+3 residues, contributing to helical fraying
- AR3 showed aromatic stacking between each i, i+4 residue, contributing to overall helicity
- AR4, which replaced position 4 NLys with NGlu on AR2, did not show the improved helicity observed between CH4 and CH5

Other Factors Promoting Helicity

Conclusions
- The phi and psi dihedral angles of the peptoids tended to congregate around previously published dihedral angles for Polyproline Type II helices.
- Peptoids capable of i, i+4 stacking are more helical.
- Aromatic stacking interactions appear to be a large driving force in peptoid folding.
- Role of aliphatic chiral side chains in promoting helicity is still unclear.

Future Directions
- Asking similar questions in this study, but designing peptoids with an i, i+4 instead of an i, i+3 stacking conformation.
- Synthesizing 2-3 peptoids in the lab.
- REST docking study with mSin3

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References
For a full list of references, please see the original publication.