Peptoid Design

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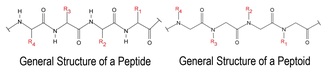
Abstract

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).

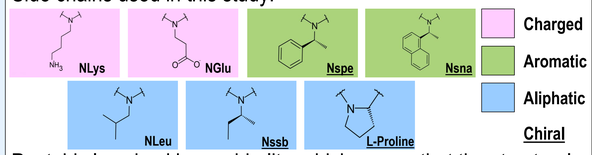
What is a Peptoid?

A peptoid is a synthetic peptide mimic:



General Structure of a Peptide General Structure of a Peptoid

Side chains used in this study:



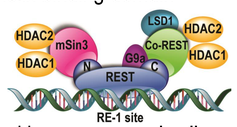
Peptoids lose backbone chirality, which means that the structural determinants will be different from that of alpha peptides

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 amphipathic alpha helix binding domain



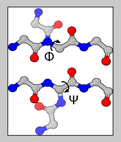
Is primarily expressed in non-neuronal cells, and is responsible for repression of genes with the RE1 DNA sequence

Has been implicated in neurodegenerative disorders, such as Huntington disease

Methods

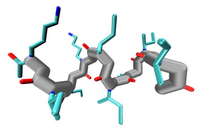
Computational Analysis
- Design of peptoid backbone with an i, i+3 stacking conformation using Avogadro Software
- Optimization of peptoid geometry using the MMFF94s force field

Quantitative Analysis
- Determination of phi (φ) and psi (ψ) dihedral angles of residues 4, 5, and 6

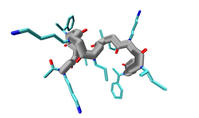


Qualitative Analysis
- Observation of overall helicity
- Visualization of side chain spread

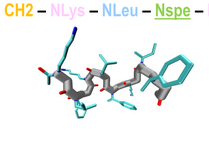
Role of Chirality in Promoting Helicity



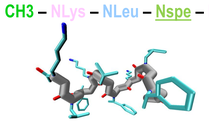
CH1 – NLys – Nssb – Nssb – NLys – Nssb – Nssb – NLys – Nssb – Nssb



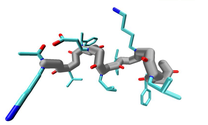
CH2 – NLys – NLeu – Nspe – NLys – Nssb – Nspe – NLys – Nssb – Nspe



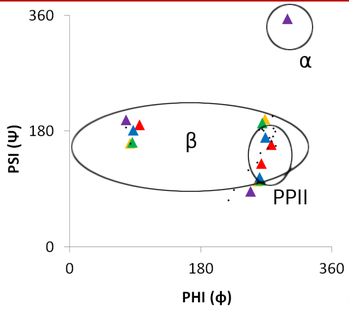
CH3 – NLys – NLeu – Nspe – NLys – NLeu – Nspe – NLys – Nssb – Nspe



CH4 – NLys – NLeu – Nspe – NLys – NLeu – Nspe – NLys – NLeu – Nspe



CH5 – NLys – NLeu – Nspe– NGlu – NLeu – Nspe – NLys – NLeu – Nspe



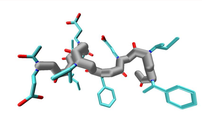
Data points represent the PHI/PSI angles on residues 4, 5, & 6 for each of the peptoids. Circled regions are consistent with literature estimates of helical types.

	%Chiral	Helicity	Fraying	Aromatic Stacking
CH1	66%	X		
CH2	56%		X	X
CH3	44%		X	X
CH4	33%	X		X
CH5	33%	X		

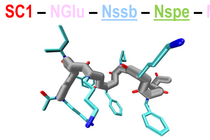
This data represents qualitative analysis of each peptoid.

- **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

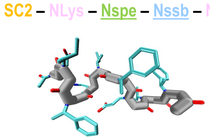
Other Factors Promoting Helicity



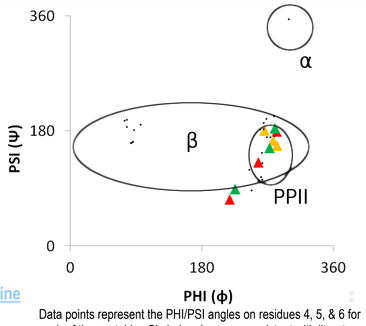
SC1 – NGlu – Nssb – Nspe – NGlu – Nssb – Nspe – NGlu – Nssb – Nspe



SC2 – NLys – Nspe – Nssb – NLys – Nspe – Nssb – NLys – Nspe – L-Proline



SC3 – NGlu – Nssb – Nspe – NLys – Nssb – Nspe – NGlu – Nssb – Nspe



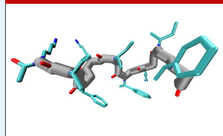
Data points represent the PHI/PSI angles on residues 4, 5, & 6 for each of the peptoids. Circled regions are consistent with literature estimates of helical types.

	Helicity	Fraying	Aromatic Stacking
SC1		X	X
SC2		X	X
SC3		X	X

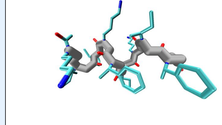
This data represents qualitative analysis of each peptoid

- The addition of L-Proline at the end of **SC2** promoted fraying
- **SC3**, which replaced position 4 NGlu with NLys on **SC1**, did not show improved helicity

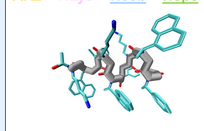
Role of Aromaticity in Promoting Helicity



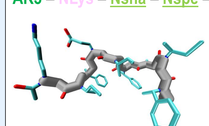
AR1 – NLys – Nssb – Nspe – NLys – Nssb – Nspe – NLys – Nssb – Nspe



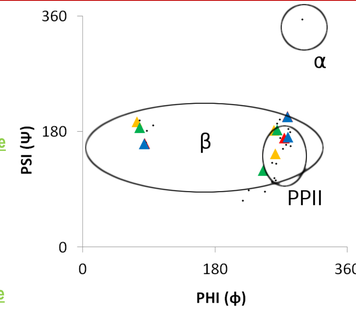
AR2 – NLys – Nssb – Nspe – NLys – Nspe – Nssb – NLys – Nssb – Nspe



AR3 – NLys – Nsna – Nspe – NLys – Nsna – Nspe – NLys – Nsna – Nspe



AR4 – NLys – Nssb – Nspe – NGlu – Nssb – Nspe – NLys – Nssb – Nspe



Data points represent the PHI/PSI angles on residues 4, 5, & 6 for each of the peptoids. Circled regions are consistent with literature estimates of helical types.

	%Aromatic	Helicity	Fraying	Aromatic Stacking
AR1	33%	X		X
AR2	33%		X	X
AR3	66%		X	X
AR4	33%	X		X

This data represents qualitative analysis of each peptoid.

- **AR1** and **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**

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

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