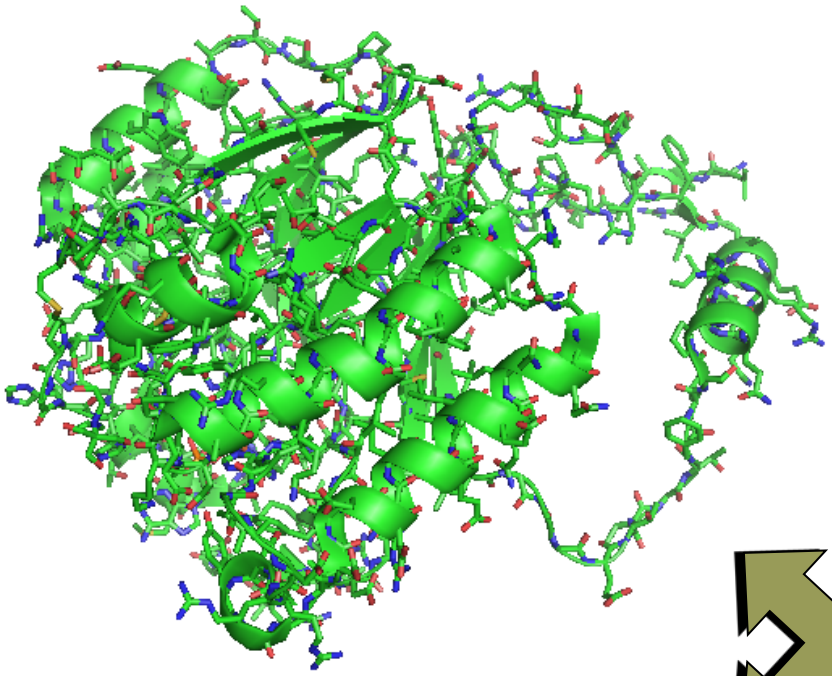
A Portrait of the Peptoid Folding Landscape:

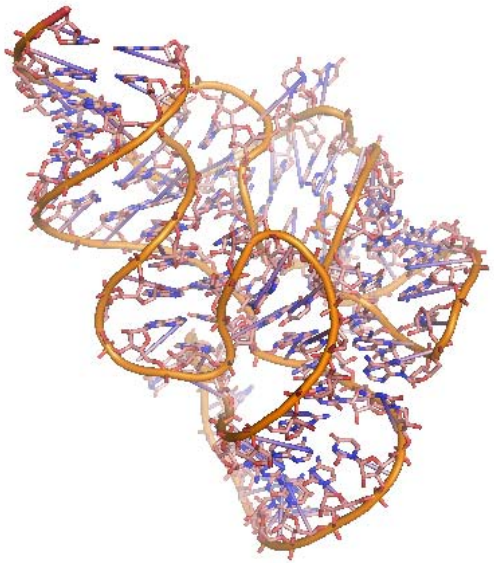
A Step Towards the Rational Design of Peptidomimetics

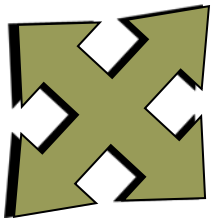
QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

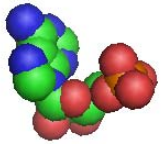
Glenn Butterfoss

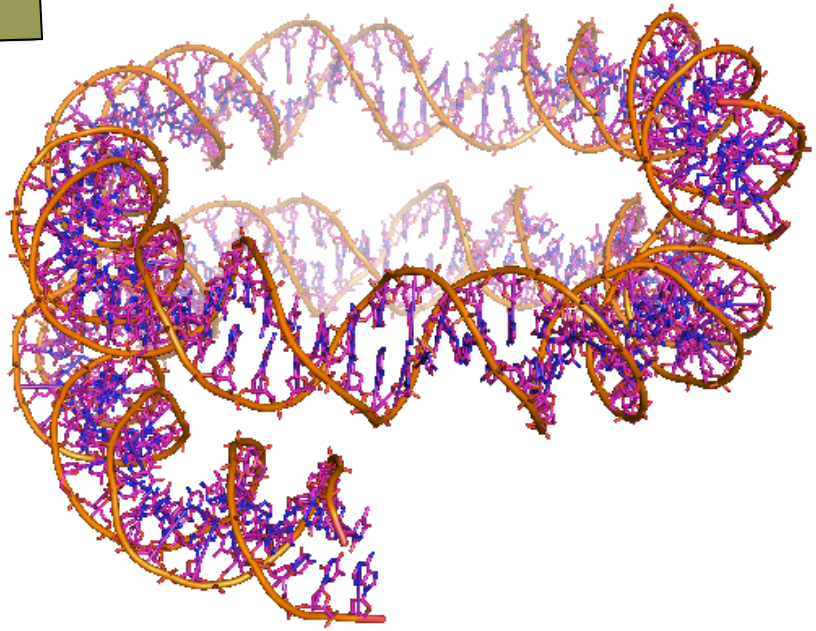
New York University





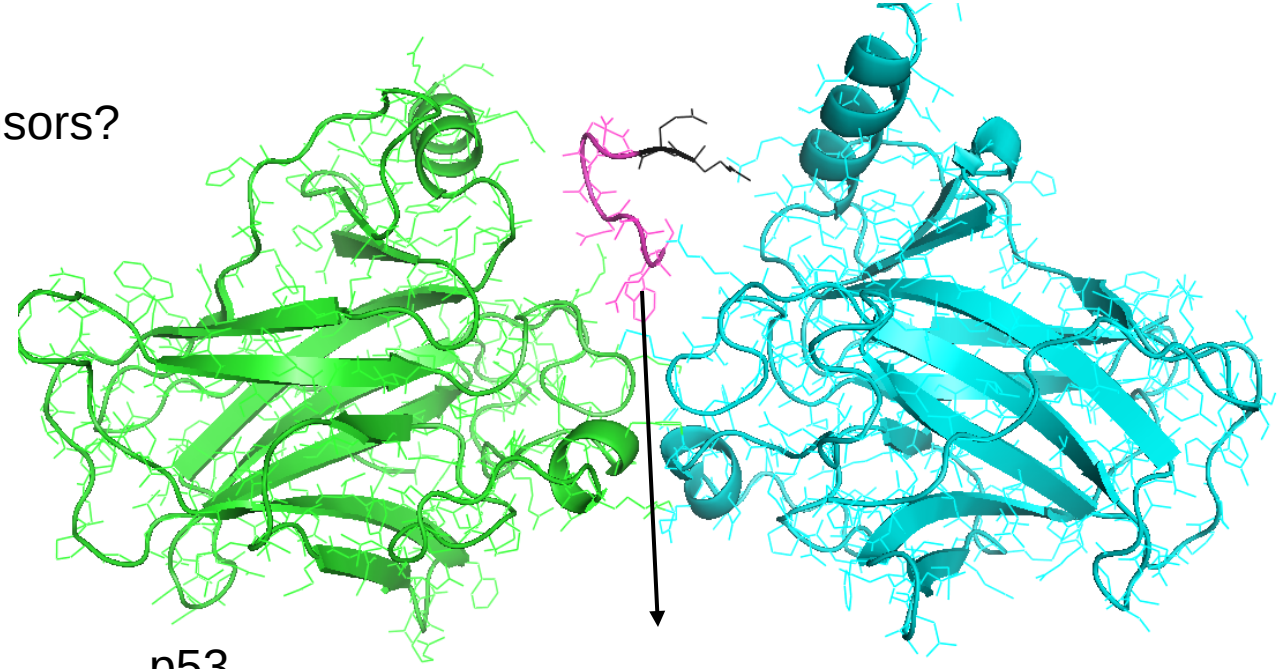




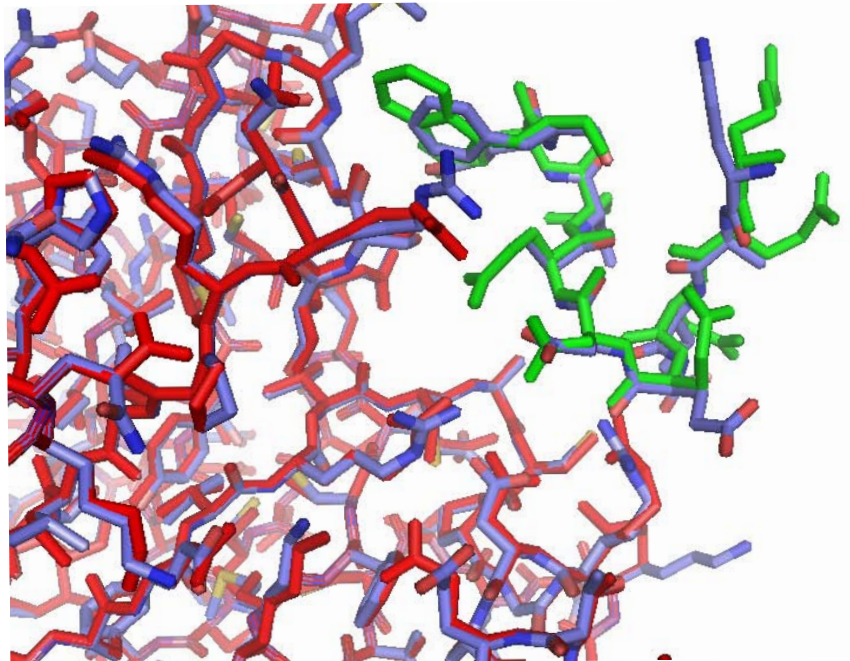


Protein Design for

Therapeutics or Biosensors?



p53



Therapeutic and biosensor molecules

Peptides

Advantages:

polymers
(easy to sample/screen)

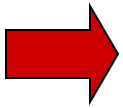
“right size”

Challenges:

degradation

alphabet size

…



Peptidomimetics

Short peptide-like molecules

Advantages:

polymers
(easy to sample/screen)

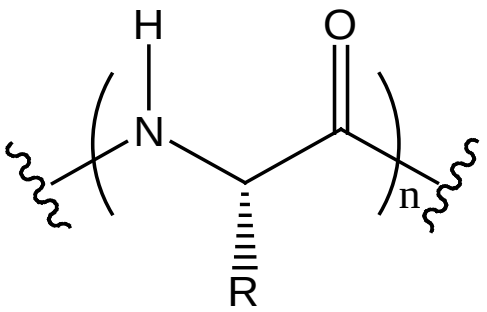
“right size”

protease resistant (?)

more customizable (?)

Therapeutic and biosensor molecules

Peptidomimetics



Peptide

Some common classes:

D-amino acids

β amino acids (extra main chain carbon)

Peptoids

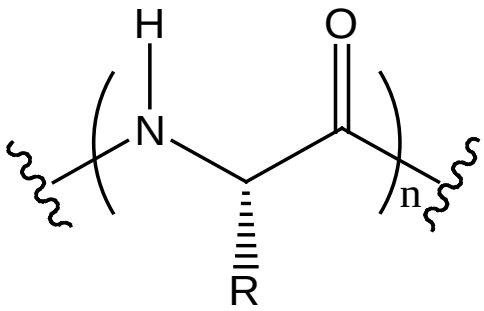
Peptoids

_N_-substituted glycine oligomers

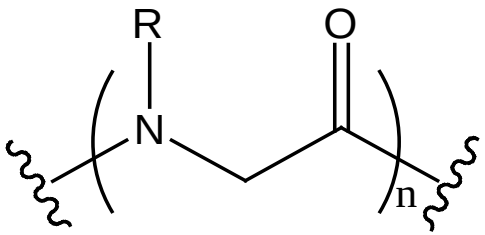
Side chain on the nitrogen

Achiral backbone

No internal backbone hydrogen-bonding



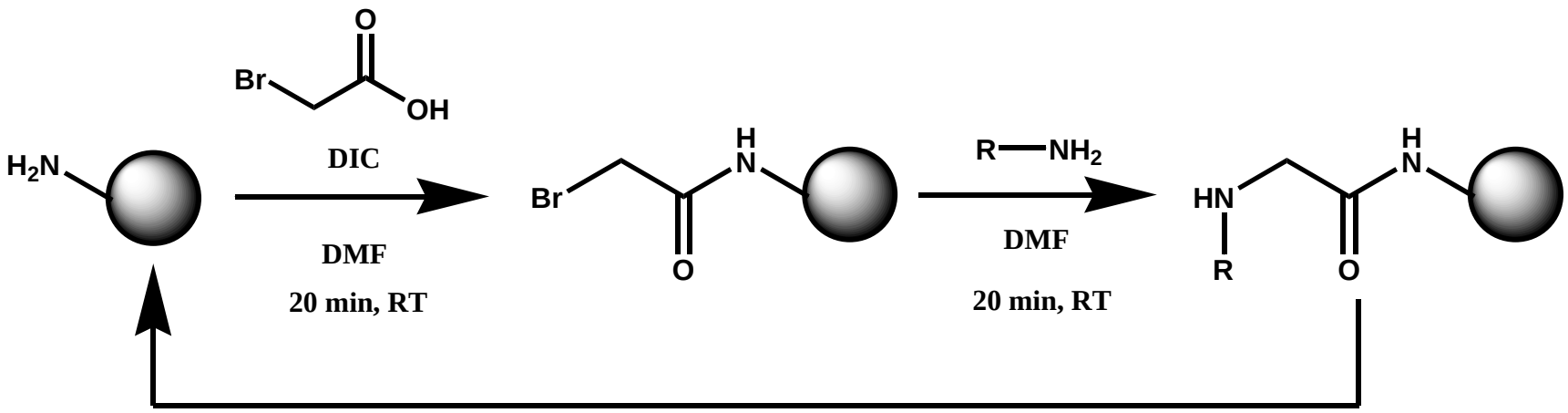
Peptide

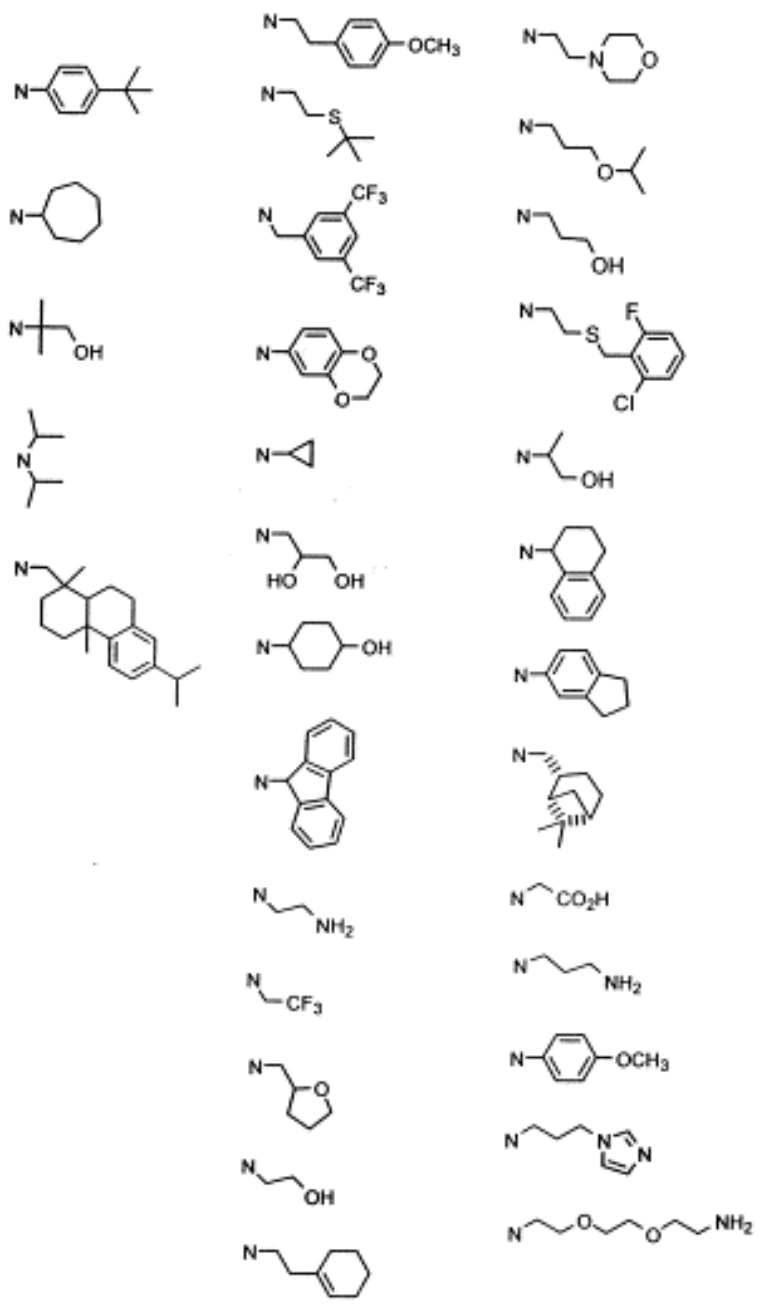


Peptoid

Peptoids:

submonomer synthesis: **very high chemical diversity**





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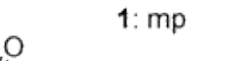

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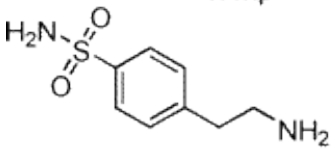

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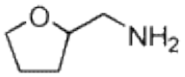
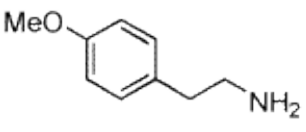


3: tf



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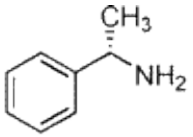
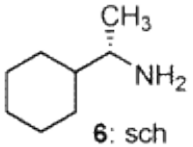


5: spe



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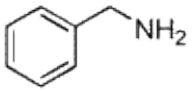
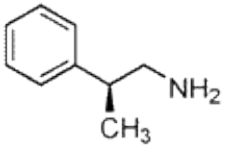
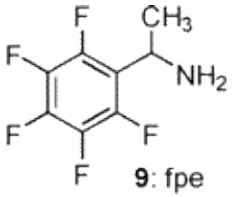


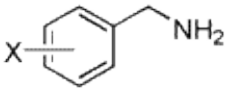
7: pm



8: spp



9: fpe

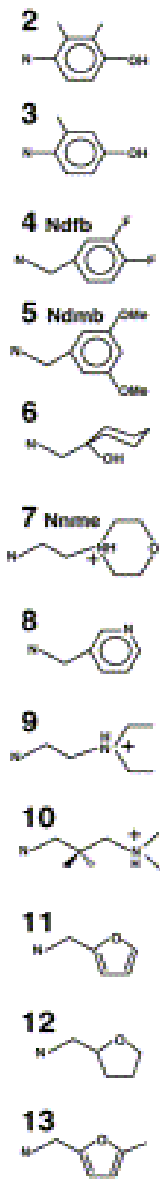


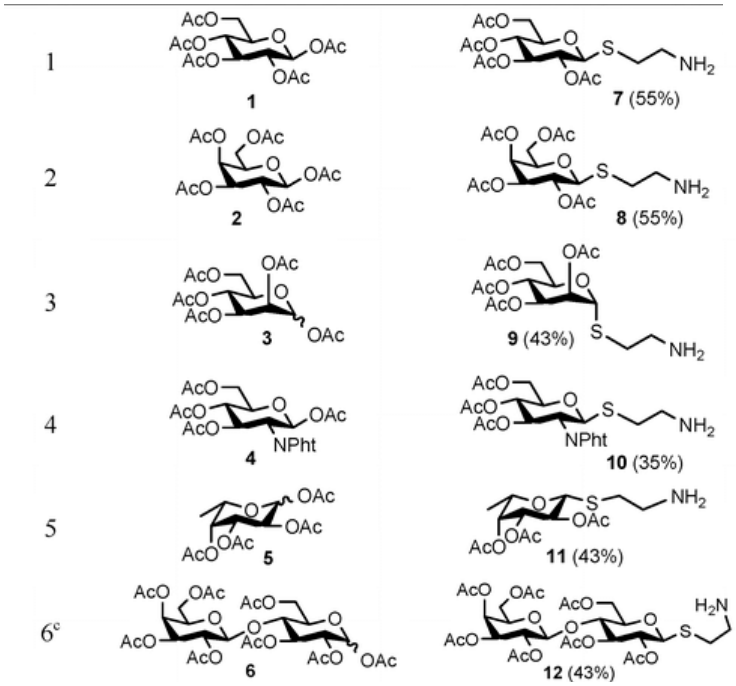
10: X=2-F; 2fb
11: X=3-F; 3fb
12: X=4-F; 4fb
13: X=2,6-F; 2,6fb
14: X=3,5-F; 3,5fb
15: X=2-NO_2; 2nb
16: X=3-NO_2; 3nb
17: X=4-NO_2; 4nb
18: X=2-Me; 2mb
19: X=4-OMe; 4mob

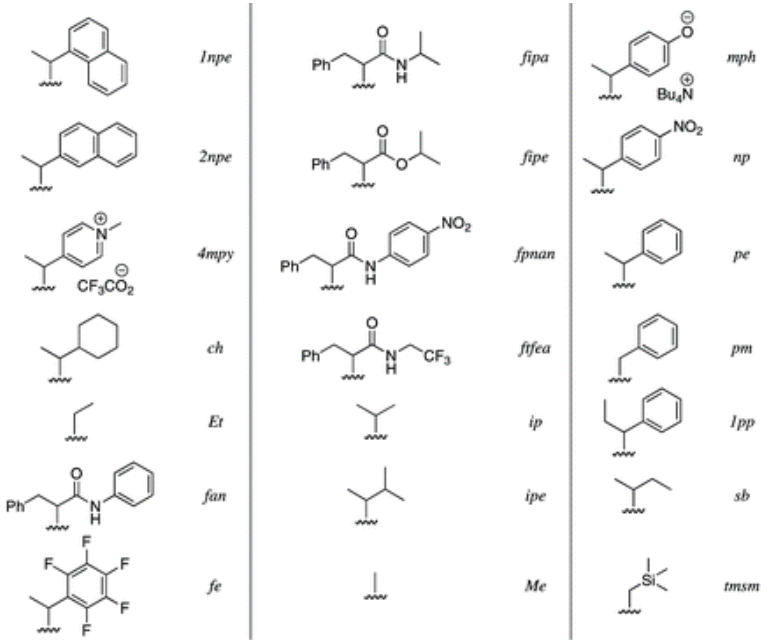
Ng, S.; Goodson, B.; Ehrhardt, A.; Moos, W. H.; Siani, M.; Winter, J. *Bioorganic & Medicinal Chemistry* **1999**, *7*, 1781-1785.

Gorske, B. C.; Jewell, S. A.; Guerard, E. J.; Blackwell, H. E. *Organic Letters* **2005**, *7*, 1521-1524.

Peptoids:





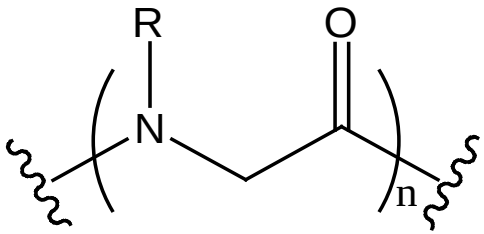


Nguyen, J. T.; Porter, M.; Amoui, M.; Miller, W. T.; Zuckermann, R. N.; Lim, W. A. *Chemistry & Biology* **2000**, *7*, 463-473.

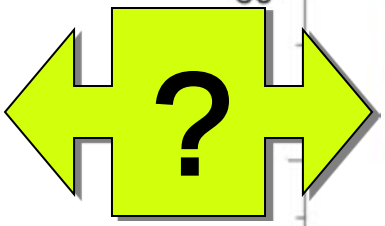
Comegna, D.; De Riccardis, F. *Organic Letters* **2009**, *11*, 3898-3901.

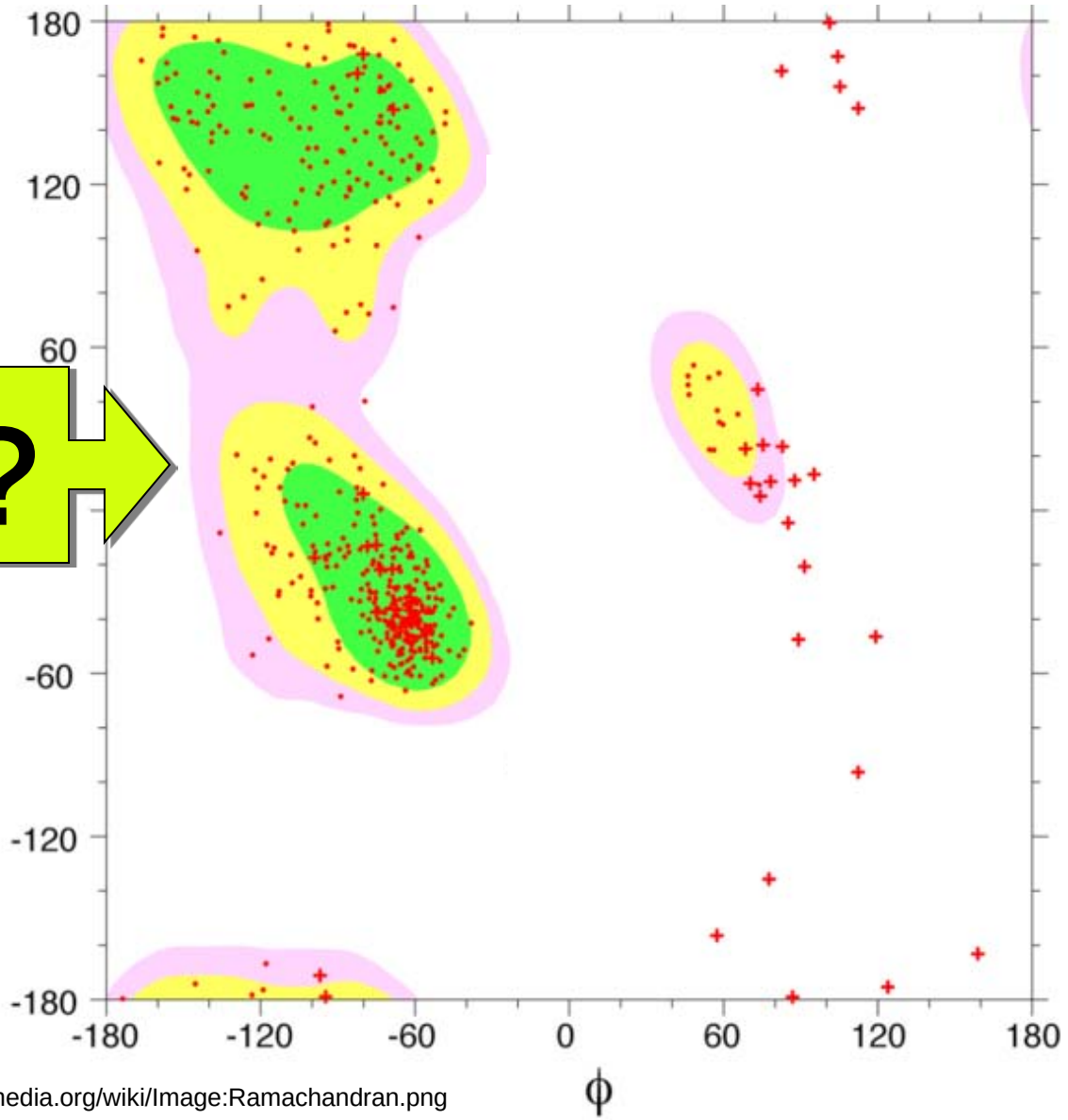
Gorske, B. C.; Stringer, J. R.; Bastian, B. L.; Fowler, S. A.; Blackwell, H. E. *Journal of the American Chemical Society* **2009**, *131*, 16555-16567.

Peptoids: designable foldamers?



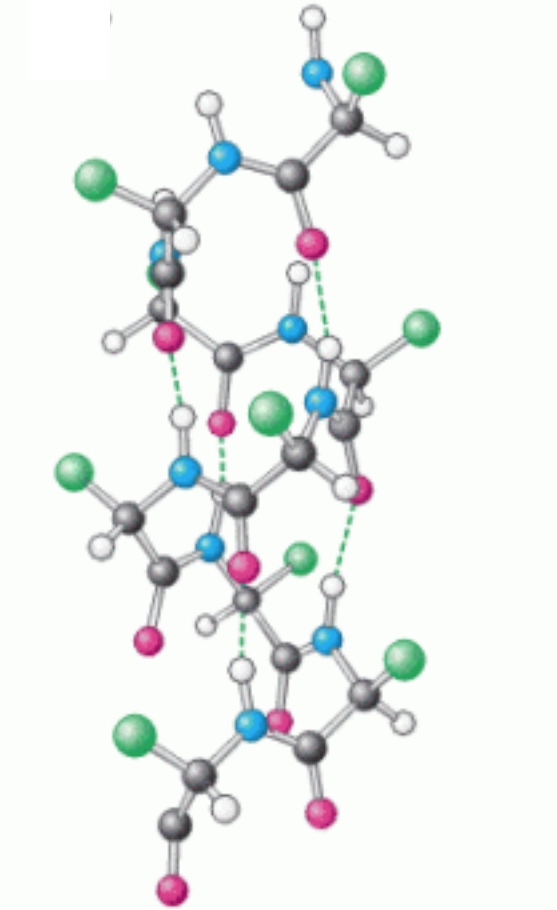
Peptoid



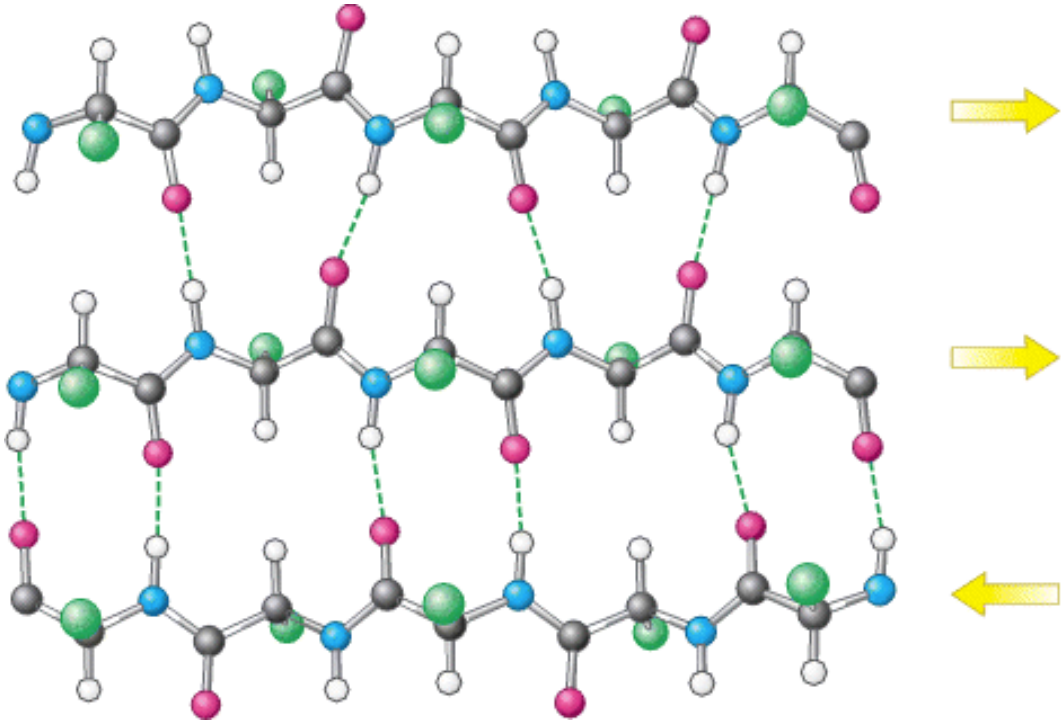


commons.wikimedia.org/wiki/Image:Ramachandran.png

Peptoids: no backbone H-bond donors:



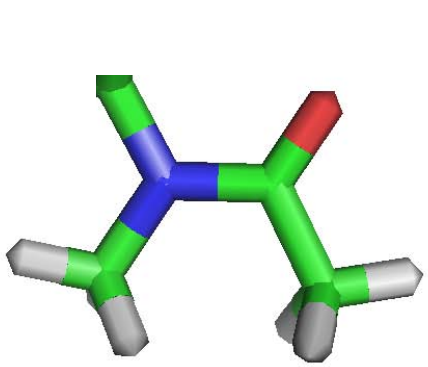
α-Helix



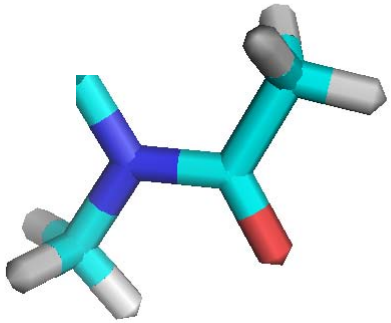
β-Sheet

Stryer's Biochemistry

Peptoids: cis/trans isomerisation

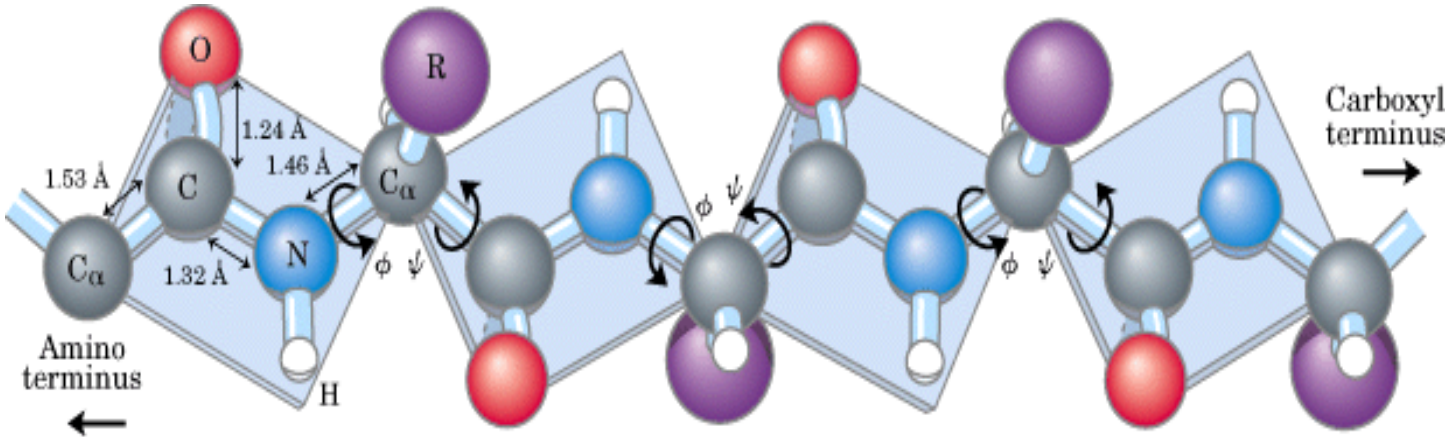


vs



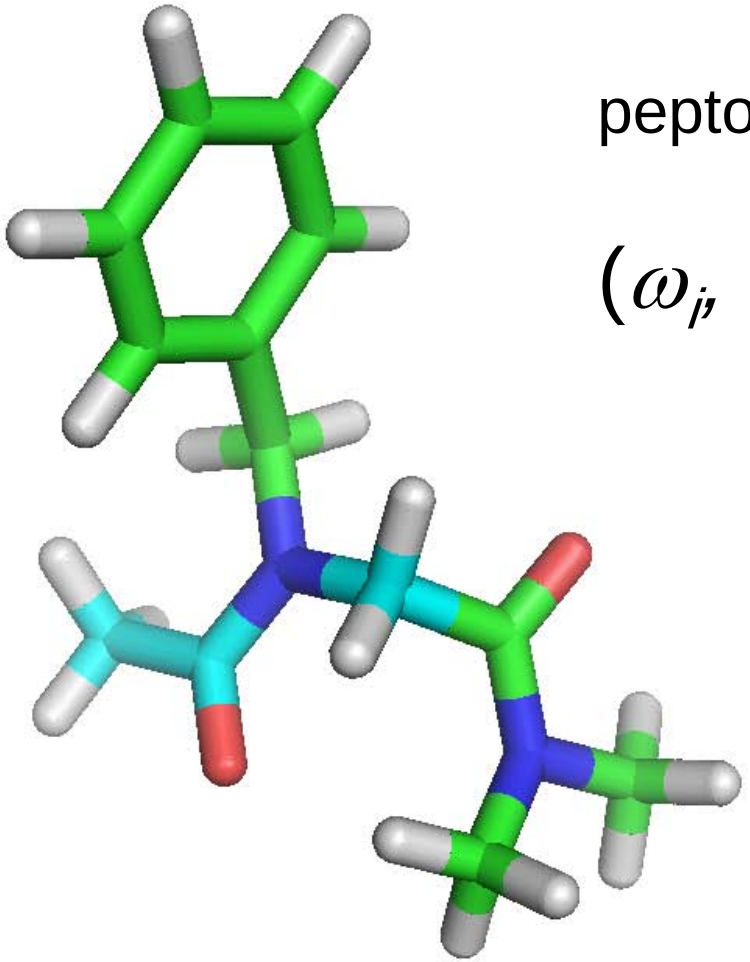
cis

trans



www.imb-jena.de/~rake/Bioinformatics_WEB/
basics_peptide_bond.html

Peptoids: cis/trans isomerisation



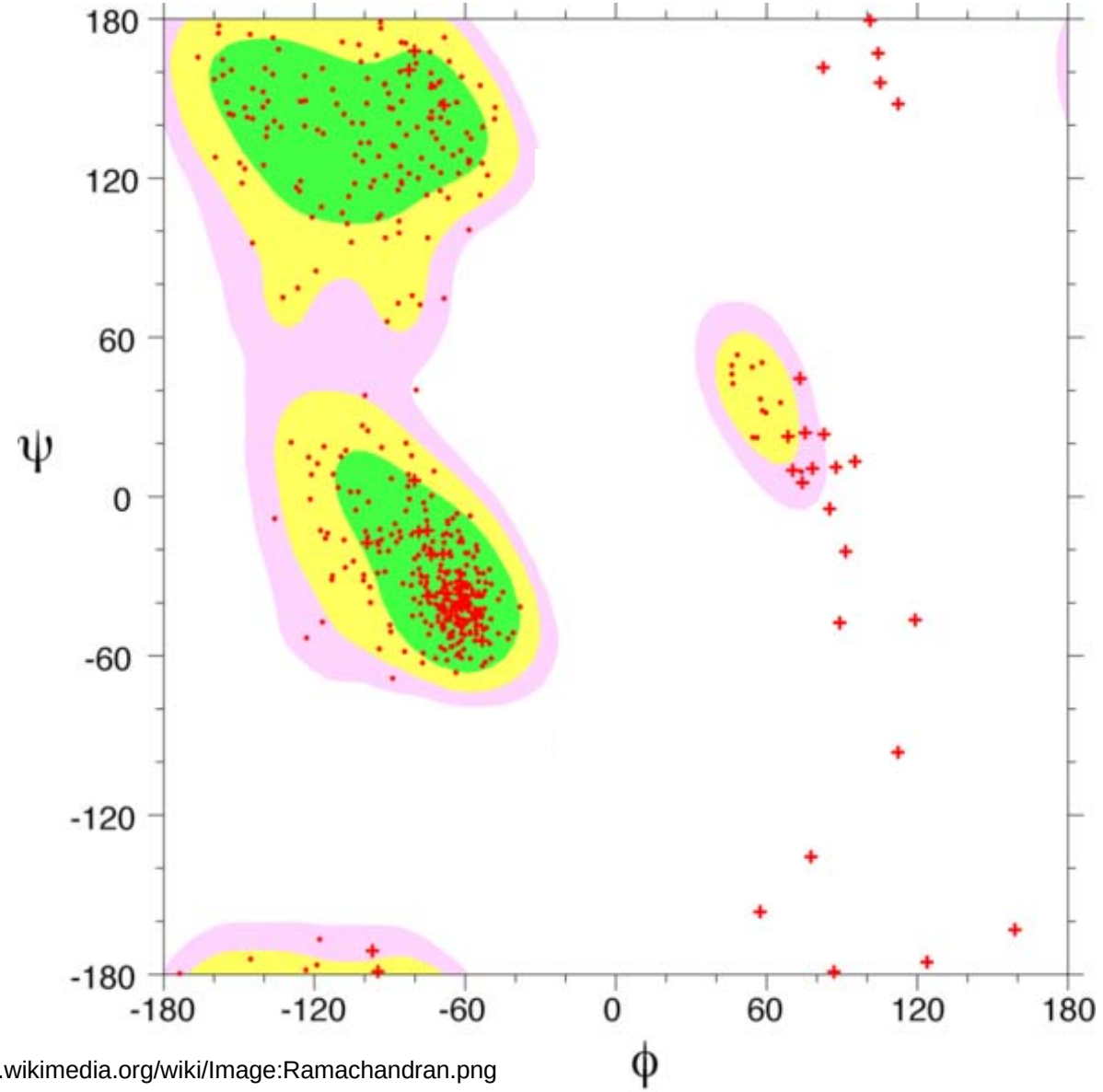
peptoid torsion indexing:

$(\omega_i, \phi_i, \psi_i)$

Peptoids: designable foldamers?

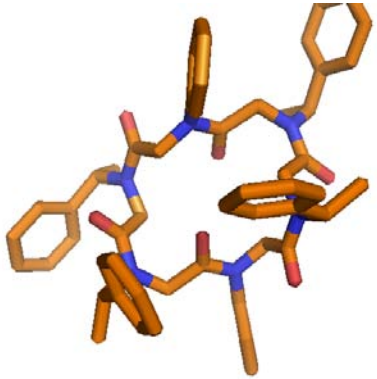
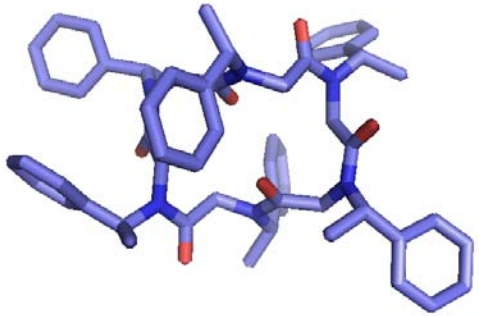
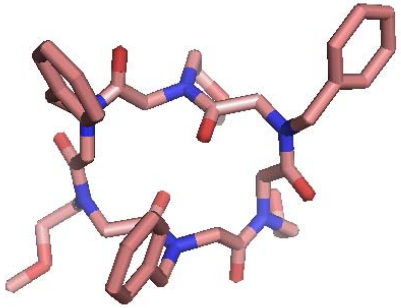
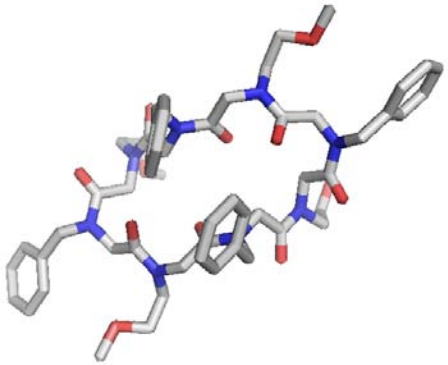
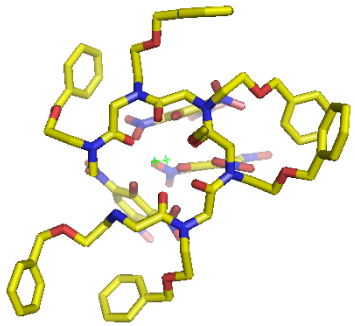
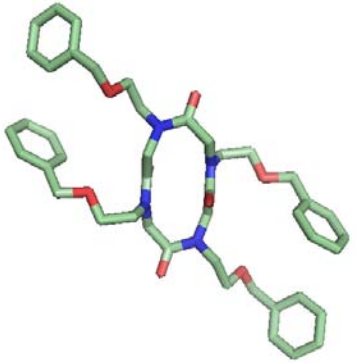
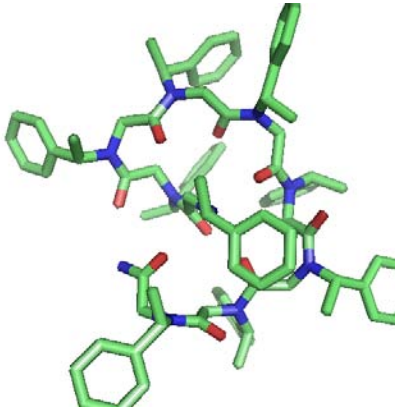
PDB: 50,000+

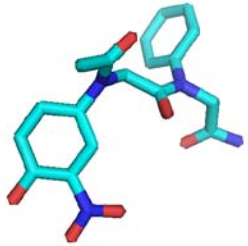
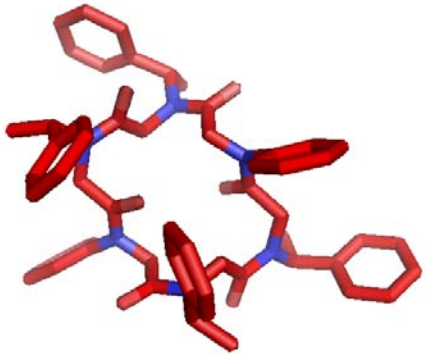
Structures



commons.wikimedia.org/wiki/Image:Ramachandran.png

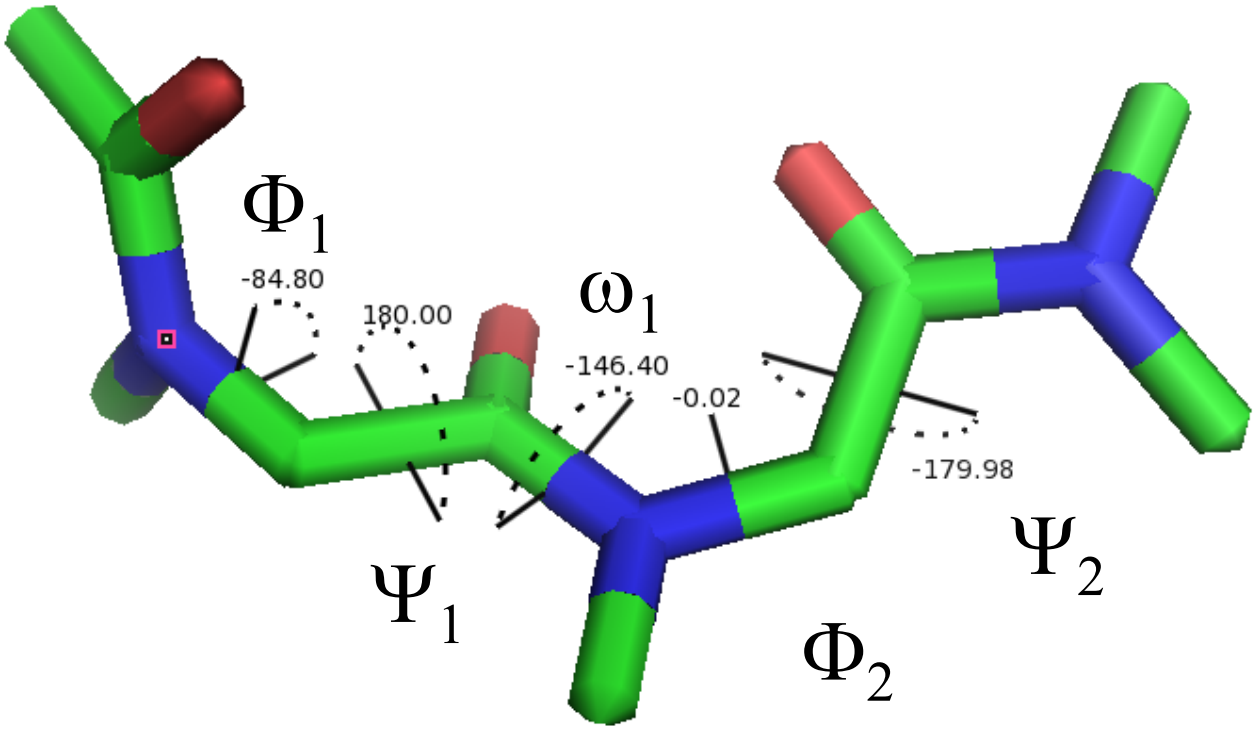
Peptoids: ~10 known structures

Peptoids: designable foldamers?

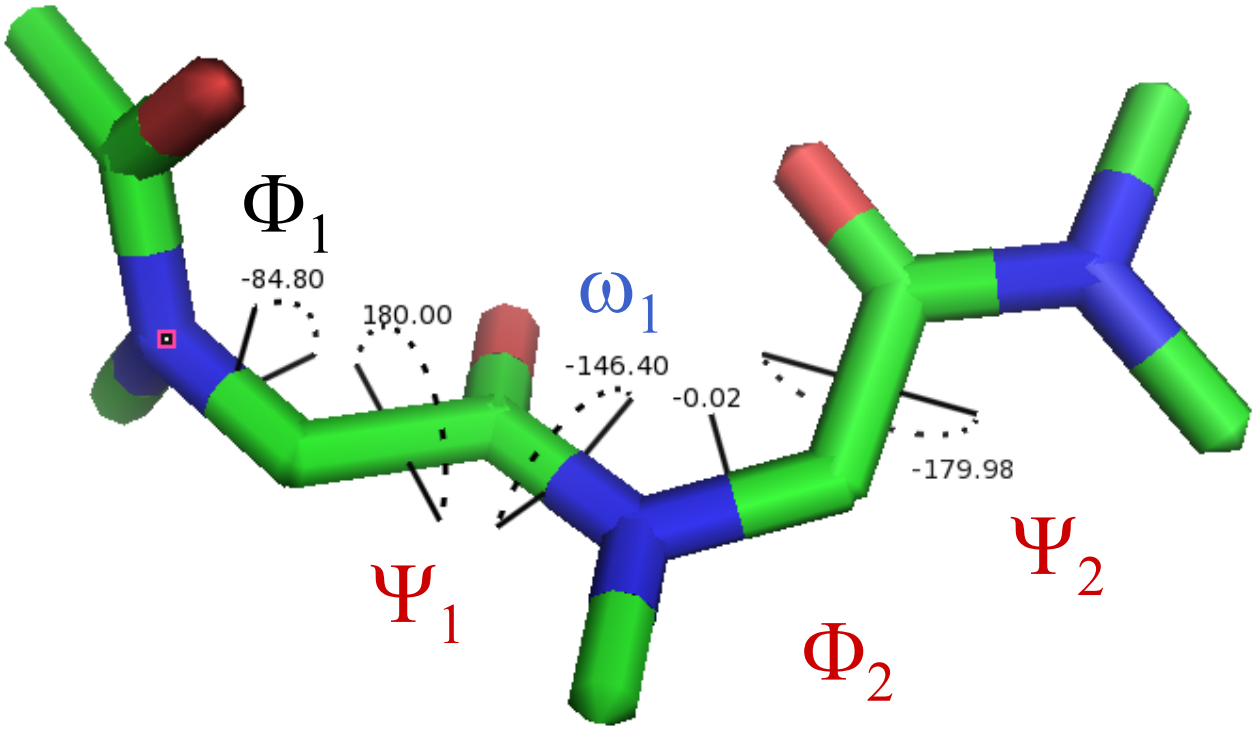
QM: Model Compound



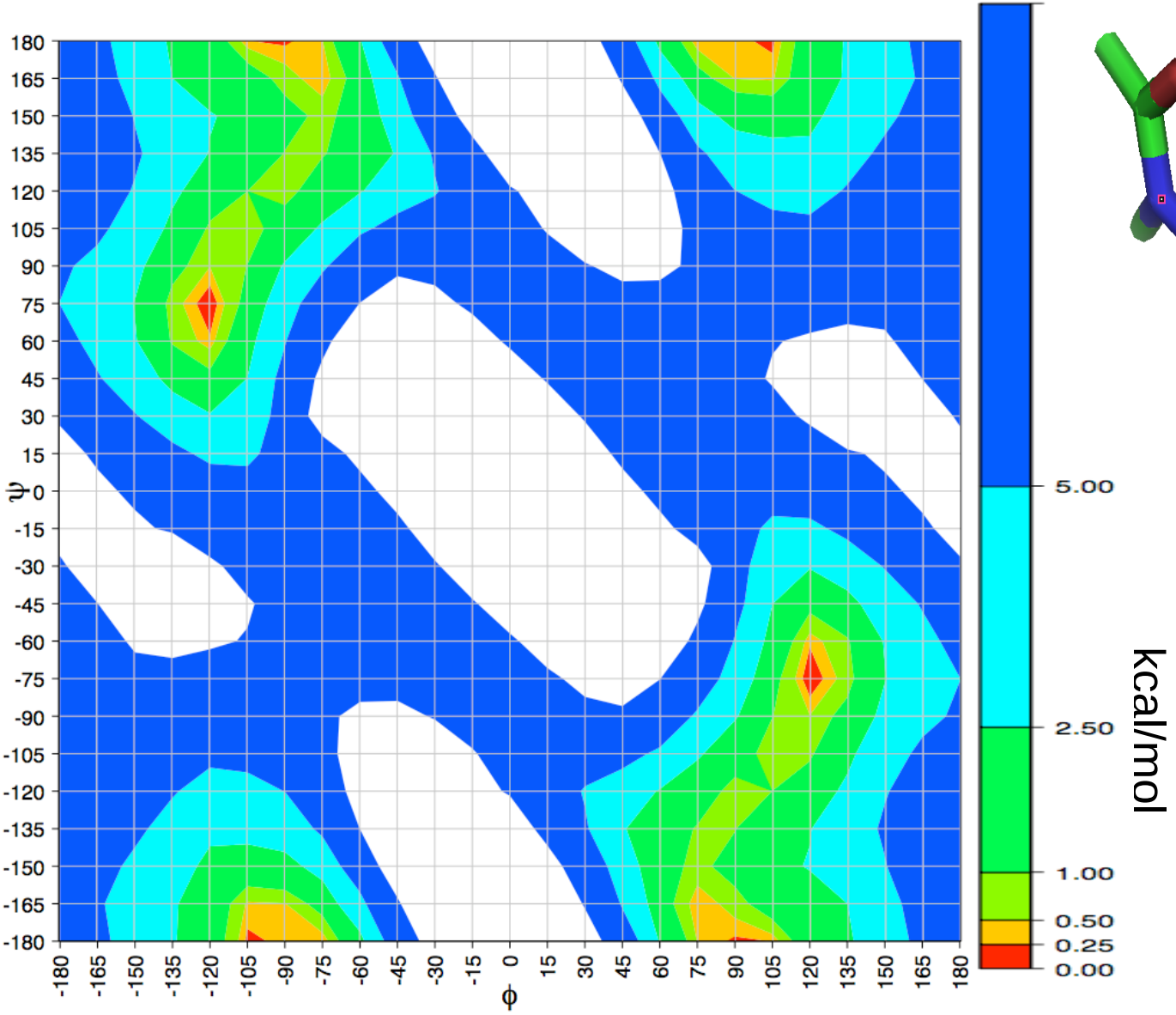
Butterfoss GL, Renfrew PD, Kuhlman B, Kirshenbaum K, Bonneau R.
J Am Chem Soc. 2009 13:16798-807.

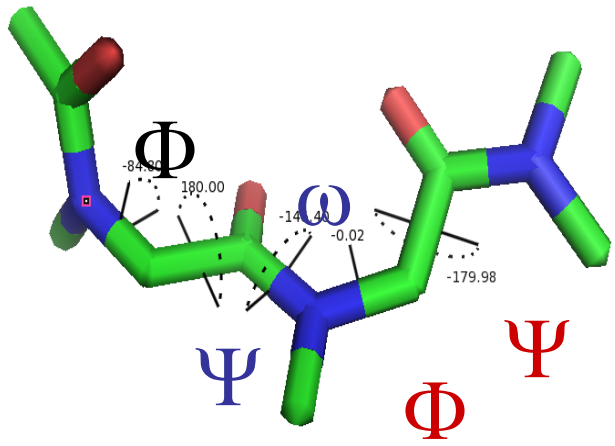
Peptoids: backbone conformational scan

Red angles - combinatorial scan every 15 deg



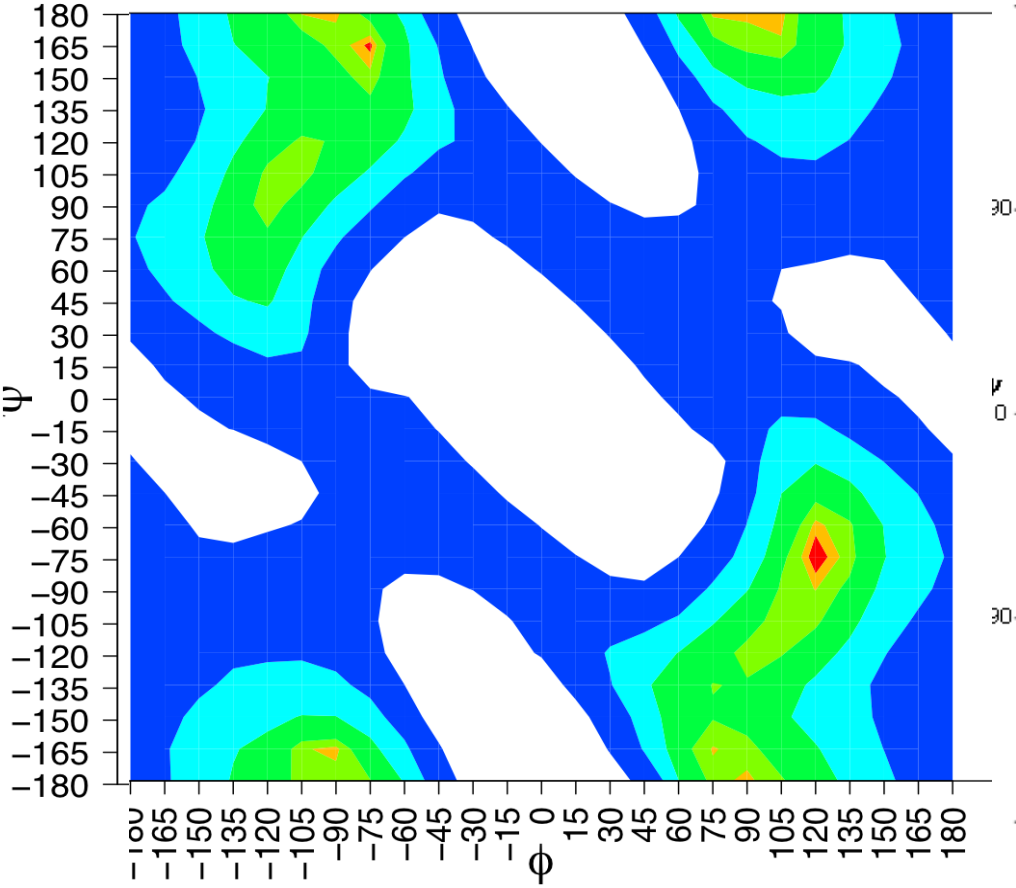
Peptoid Ramachandran energy surface



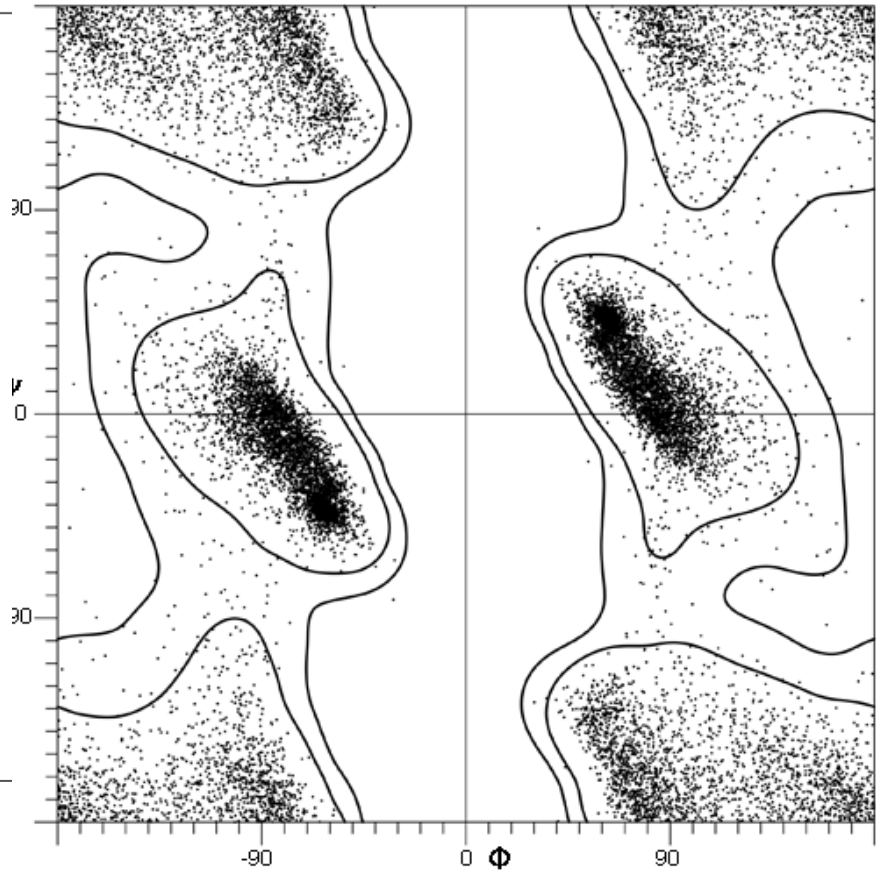


trans

Peptoid Ramachandran energy surface

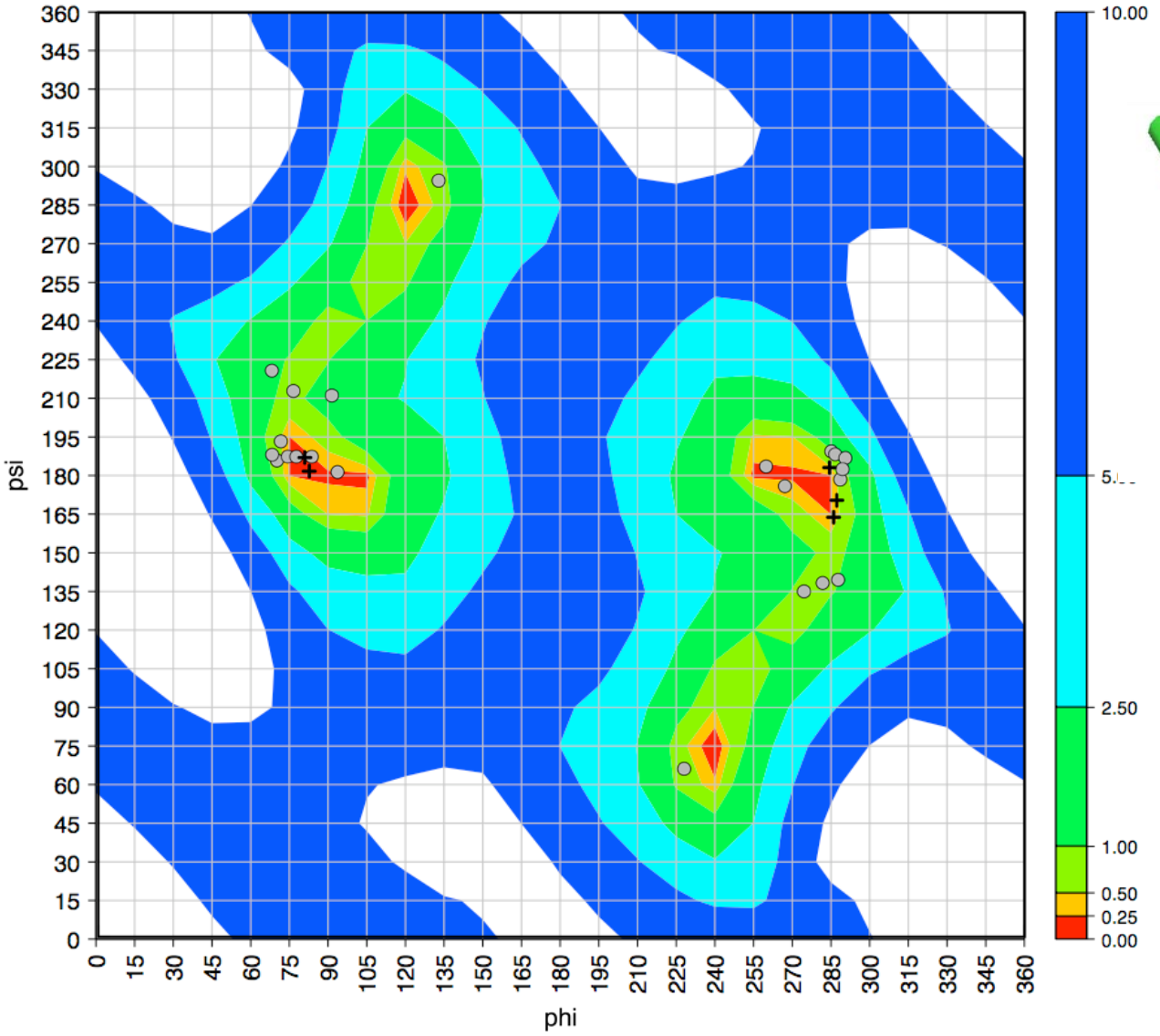


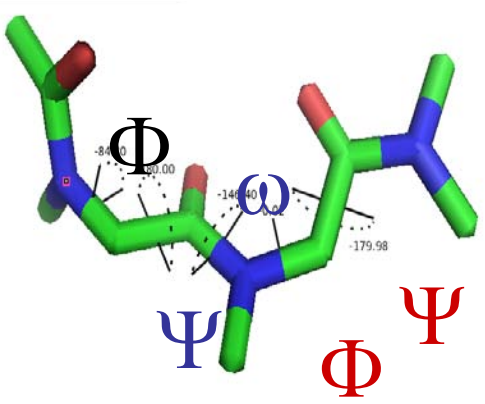
trans



glycine

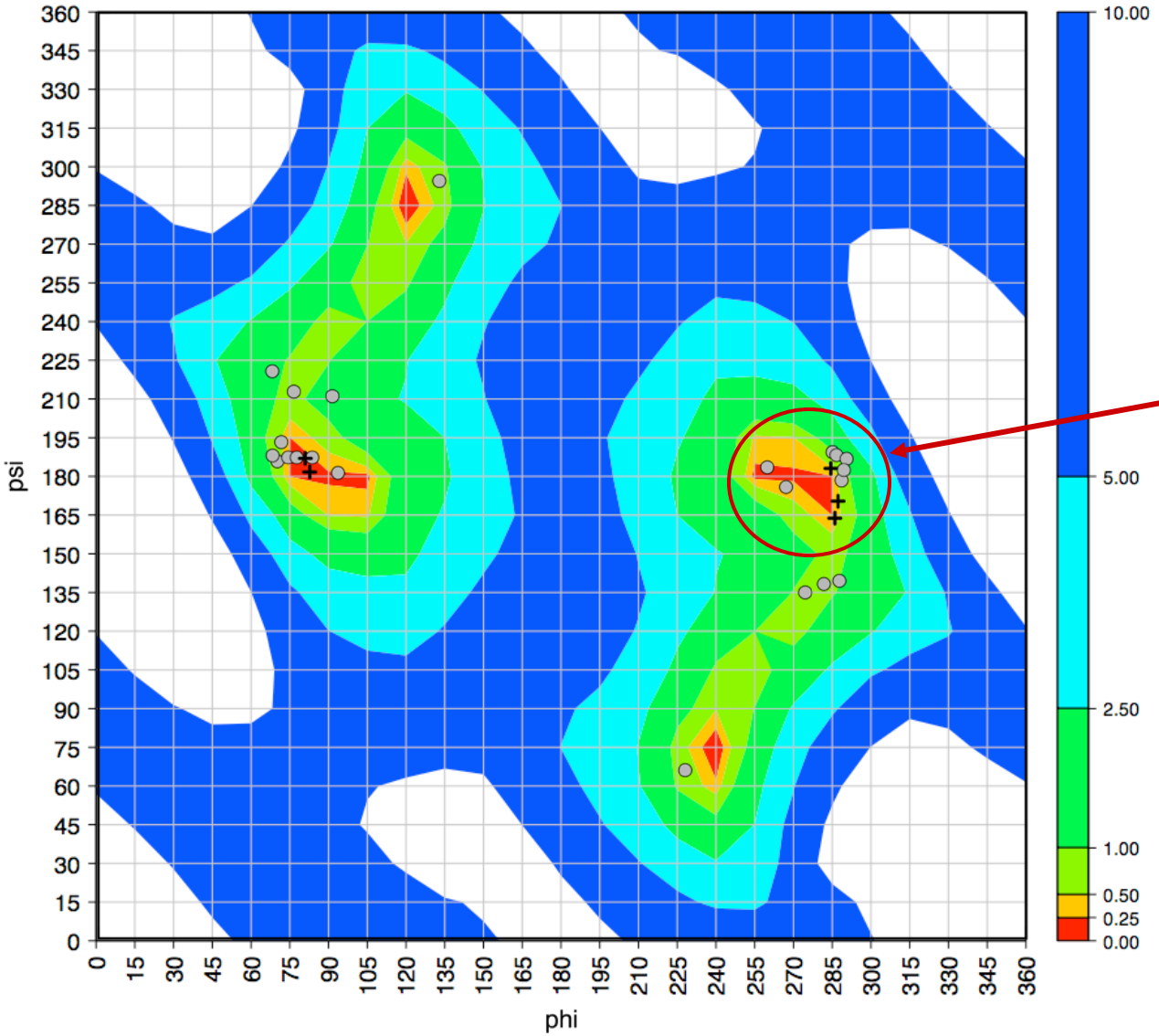
Peptoid Ramachandran energy surface





trans

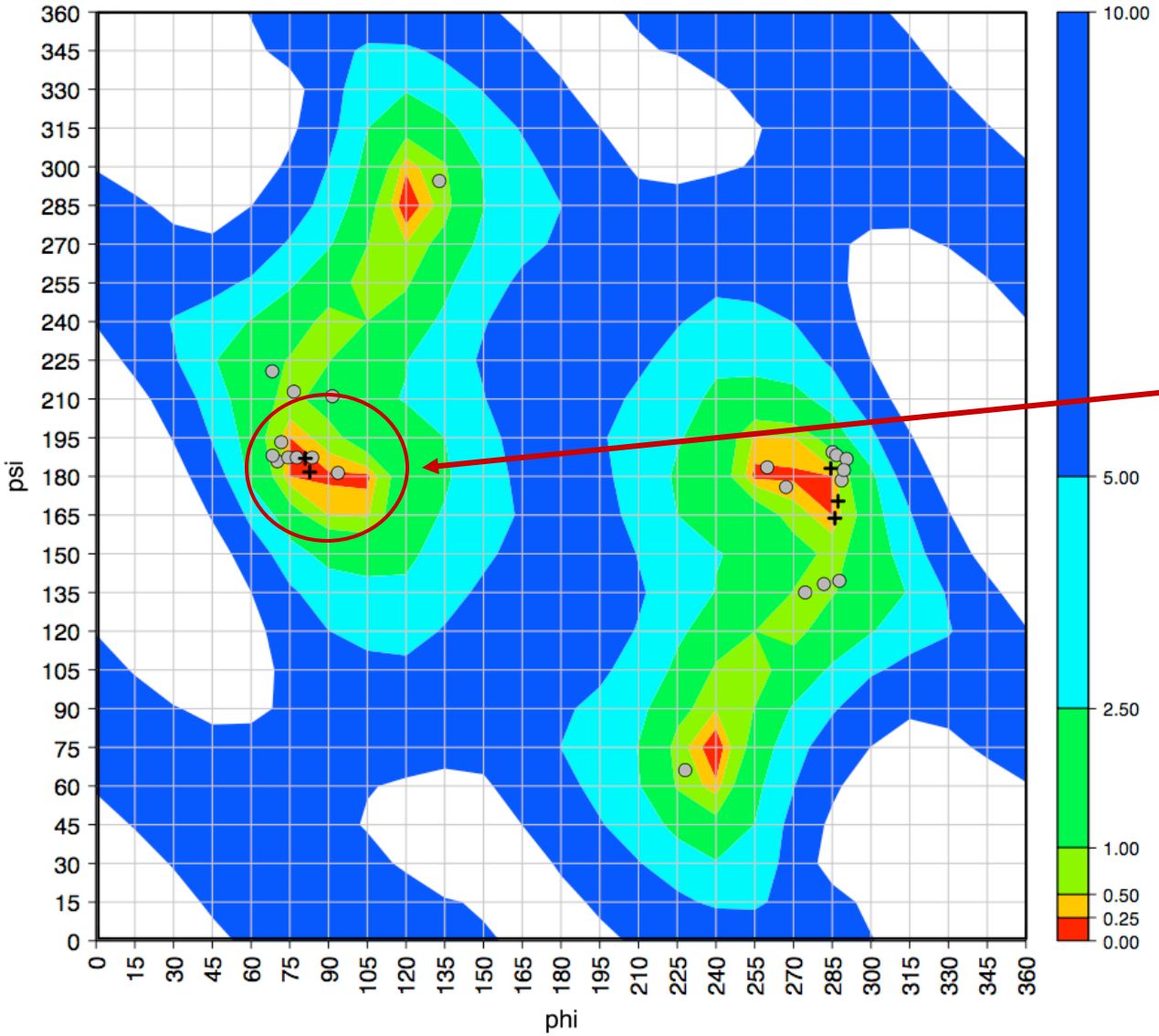
Peptoid Ramachandran energy surface



PPII helix

trans

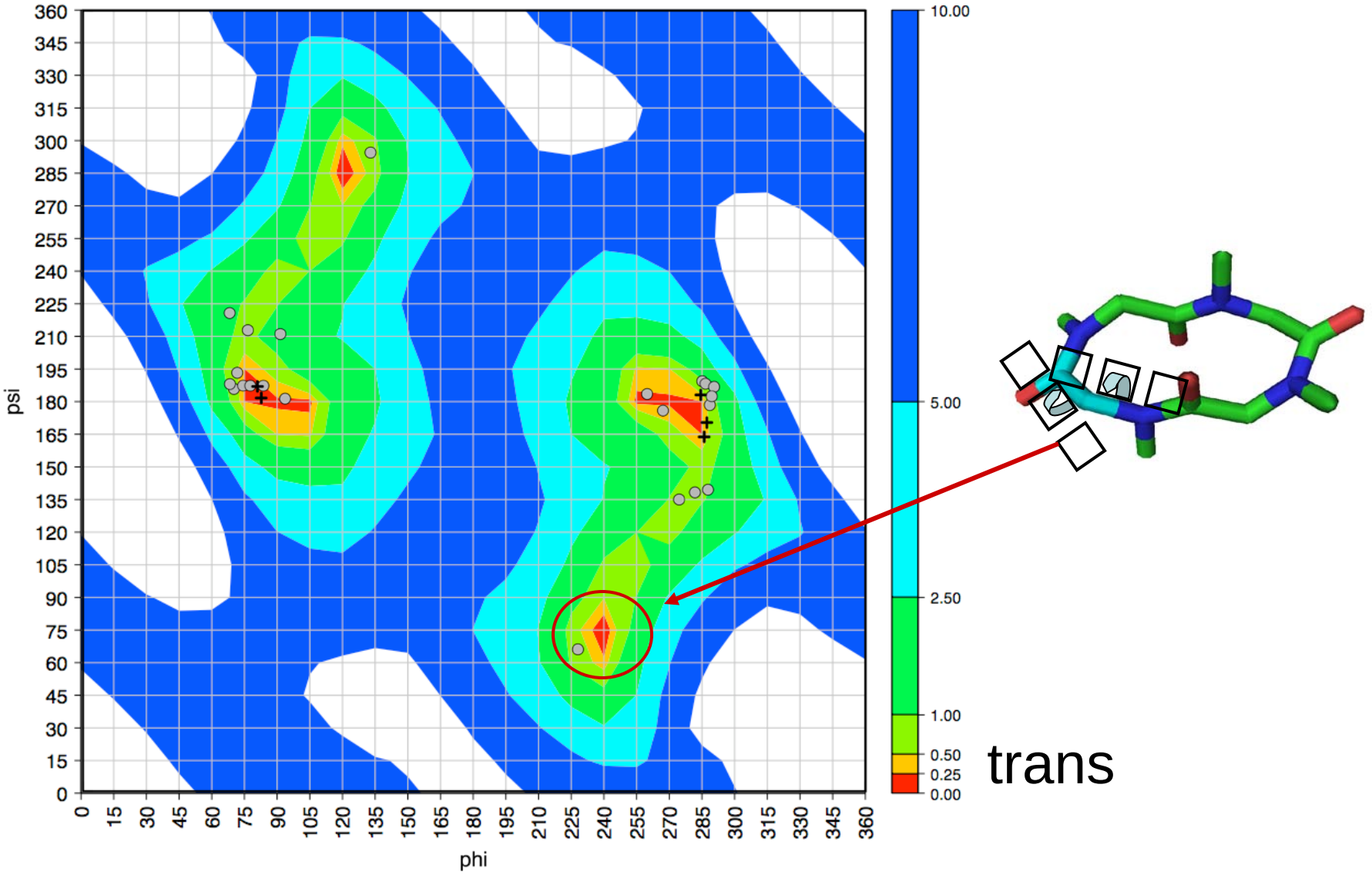
Peptoid Ramachandran energy surface



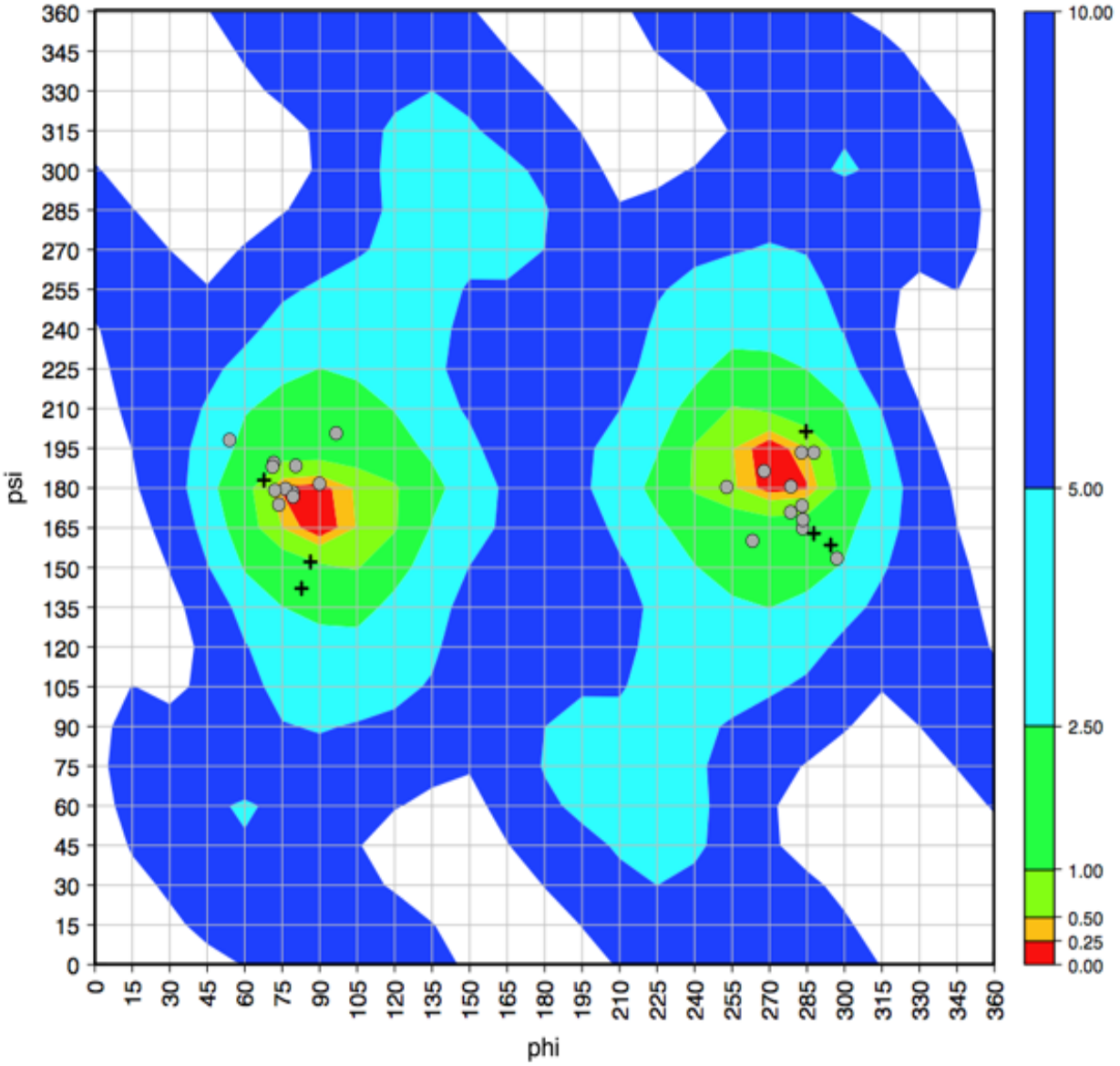
PPII helix
mirror image
(right handed)

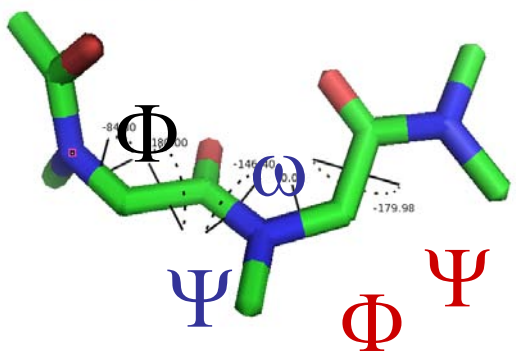
trans

Peptoid Ramachandran energy surface



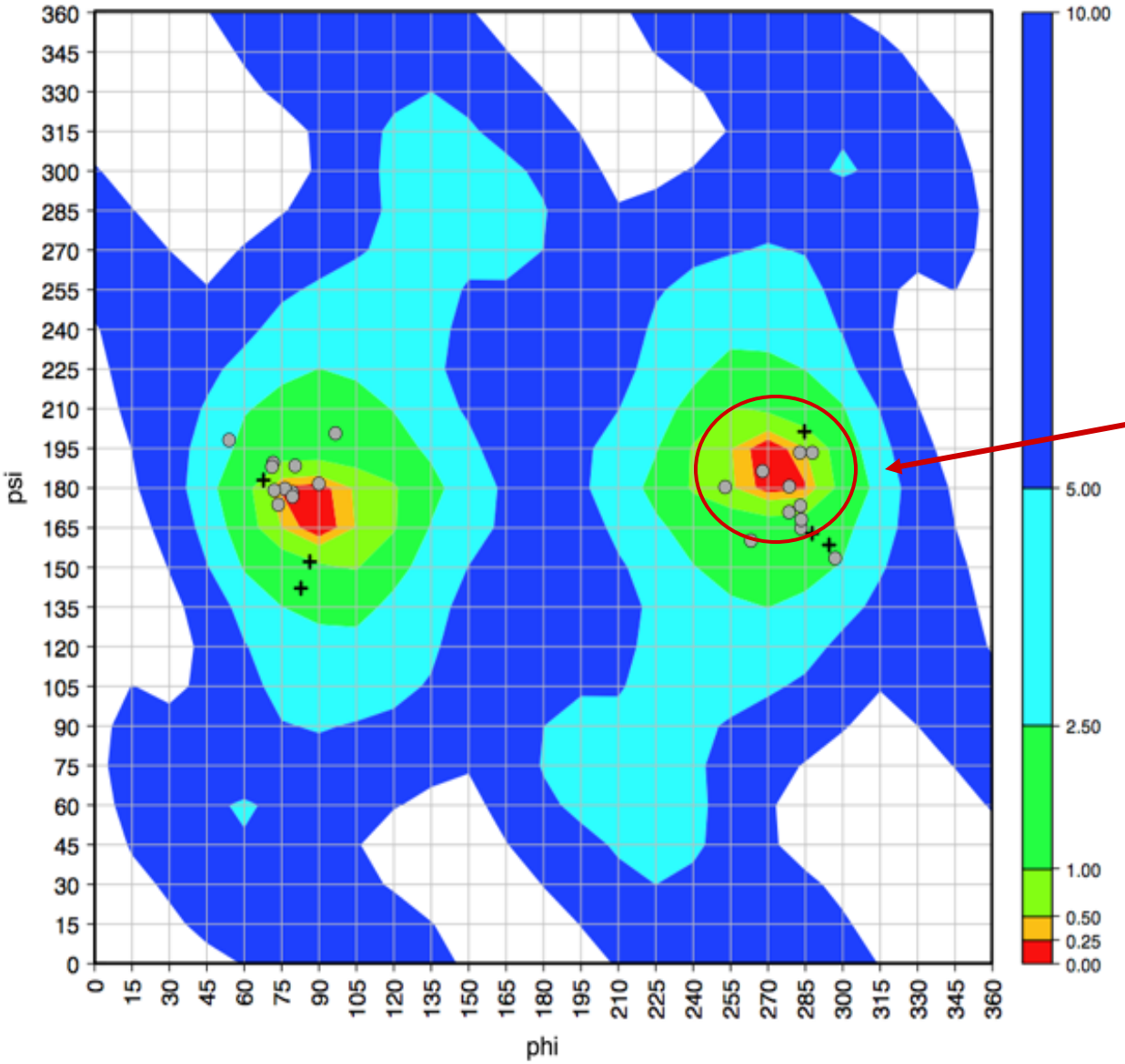
Peptoid Ramachandran energy surface





cis

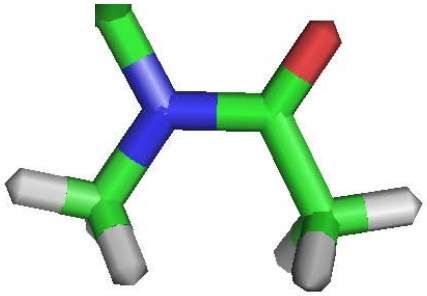
Peptoid Ramachandran energy surface



PPI helix

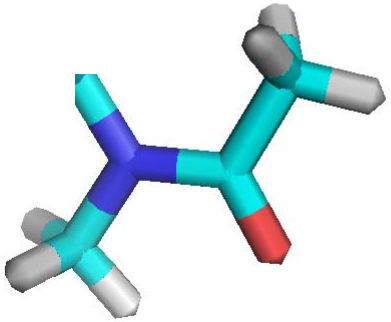
cis

Peptoid amide isomerization:



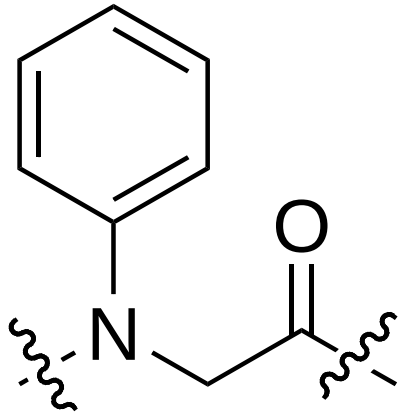
cis

vs



trans

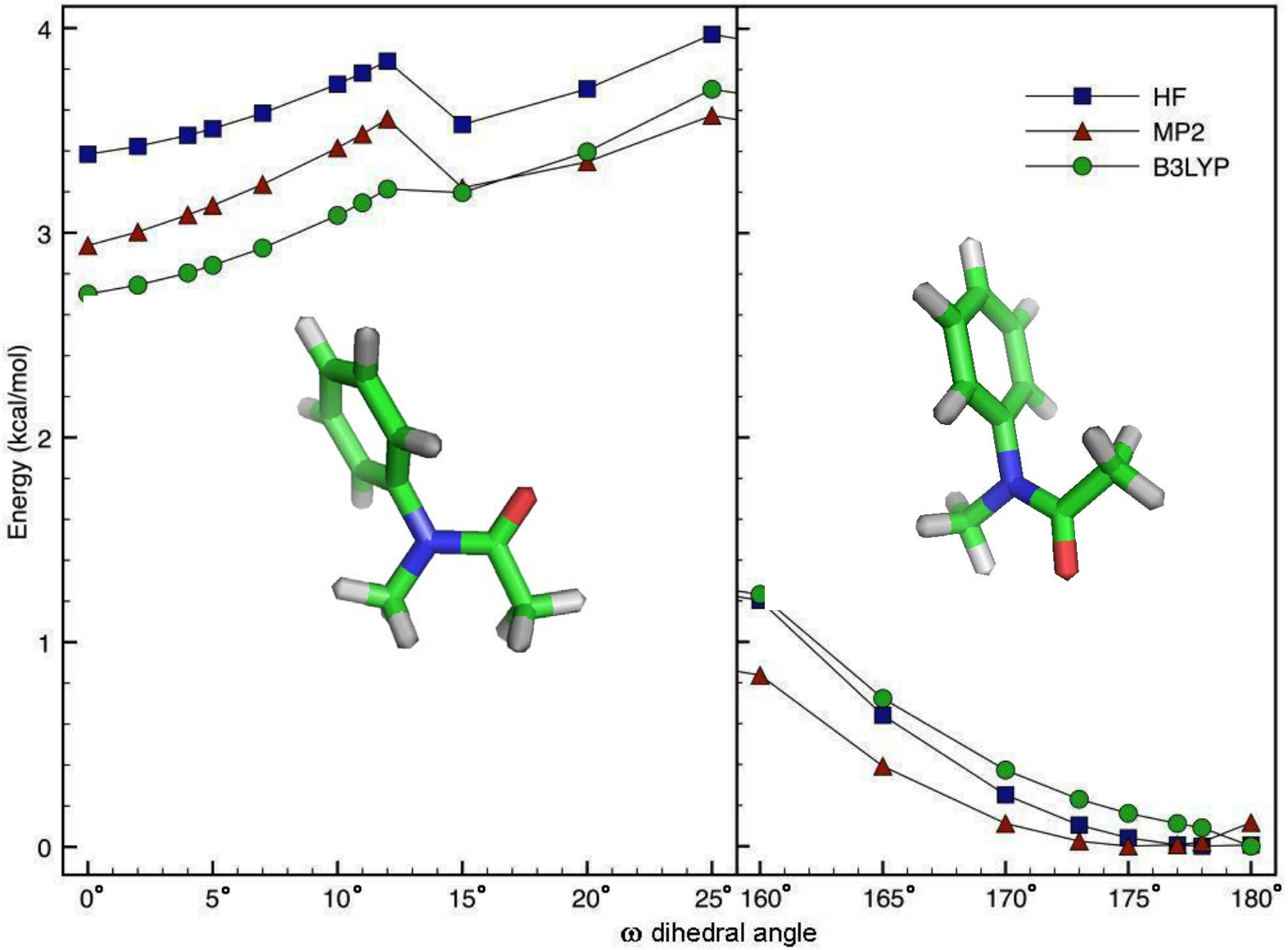
Peptoids: *N*-aryl side chains



Shah NH, Butterfoss GL, Nguyen K, Yoo B, Bonneau R, Rabenstein DL, Kirshenbaum K.
J Am Chem Soc. 2008 130: 16622-32.

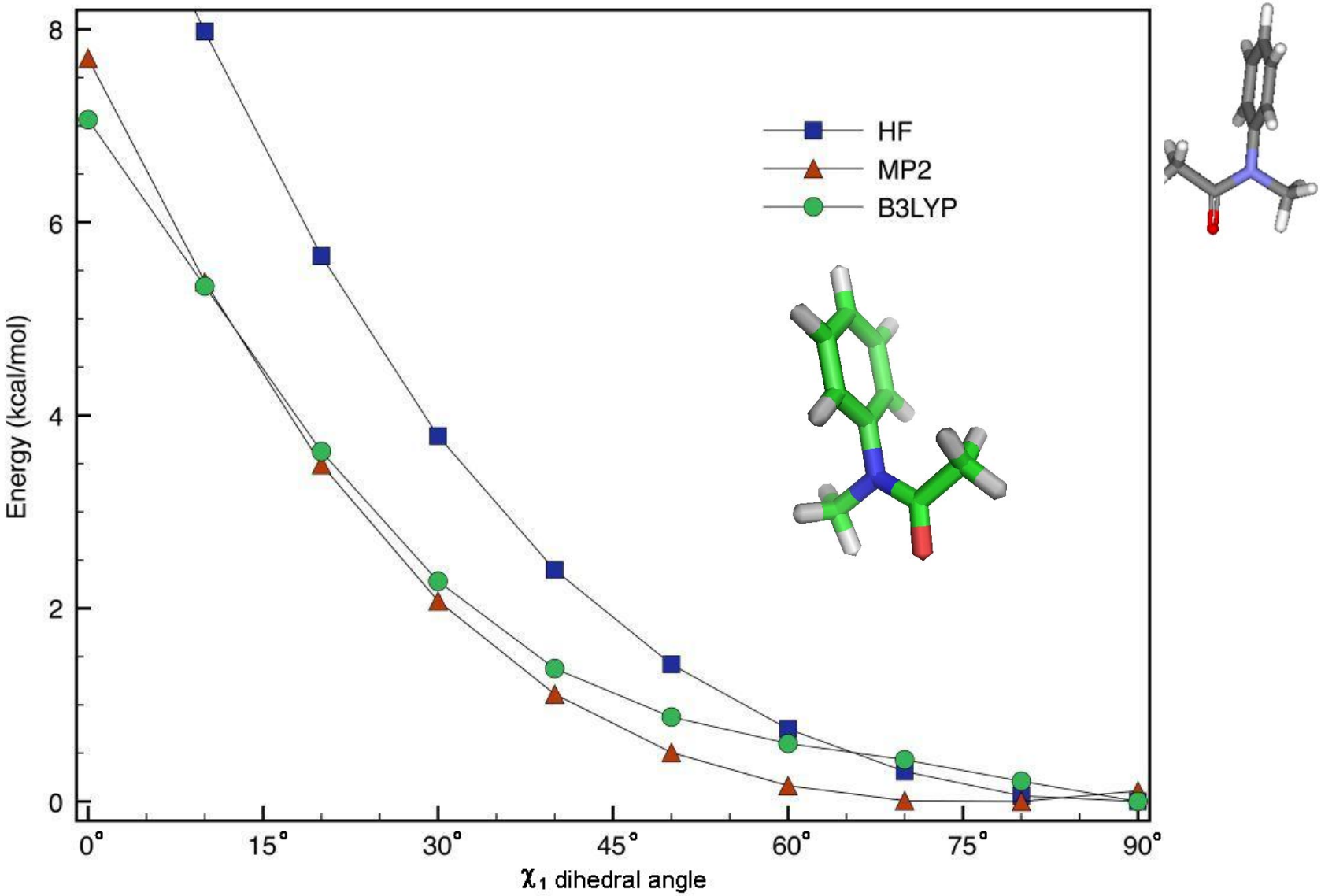
Peptoids: *N*-aryl side chains

Monomer prefers trans (consistent with NMR data)



Peptoids: *N*-aryl side chains

Chi1 prefers 90˚

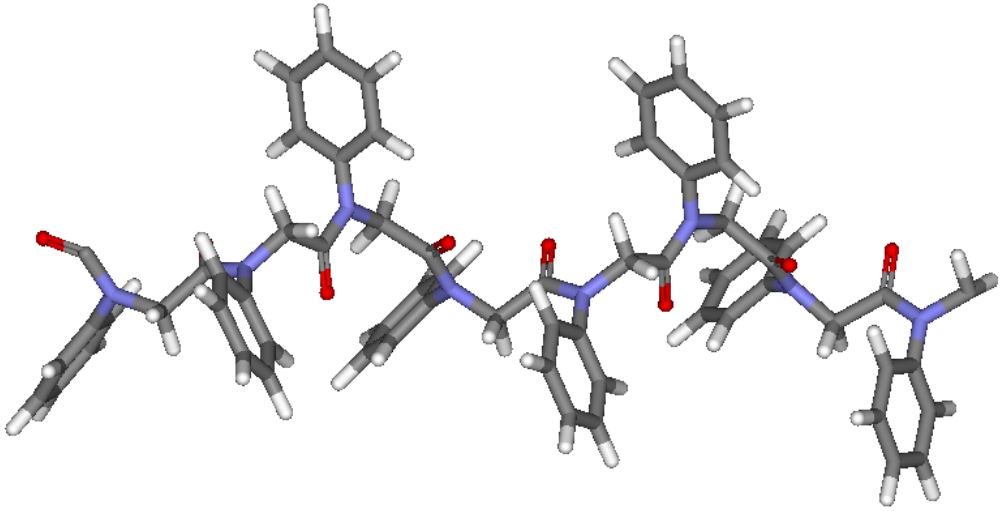


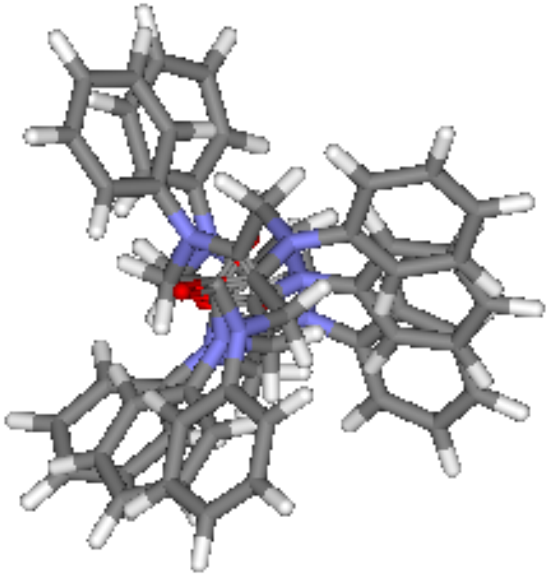
Peptoids: *N*-aryl side chains

Predicted model of N-aryl polymer: ~PPII helix

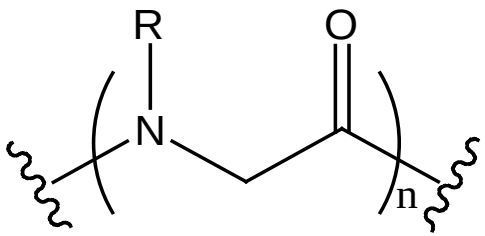
(φ,ψ) (-75°, 150°)

3-3.3 residues per turn





Peptoids in Rosetta



Peptoid

Issues:

Non canonical backbone & side chains

MM Energy functions

chi 1

cis / trans isomerization

movers & rotamer libraries

Peptoids in Rosetta: Energy Function Modifications

Unmodified Terms

Inter-residue Lennard-Jones

Hydrogen Bond term

Solvation term

Add

MM torsion term

MM intra residue LJ term

Explicit unfolded

Remove

Dunbrack internal energy term

Ramachandran backbone torsion

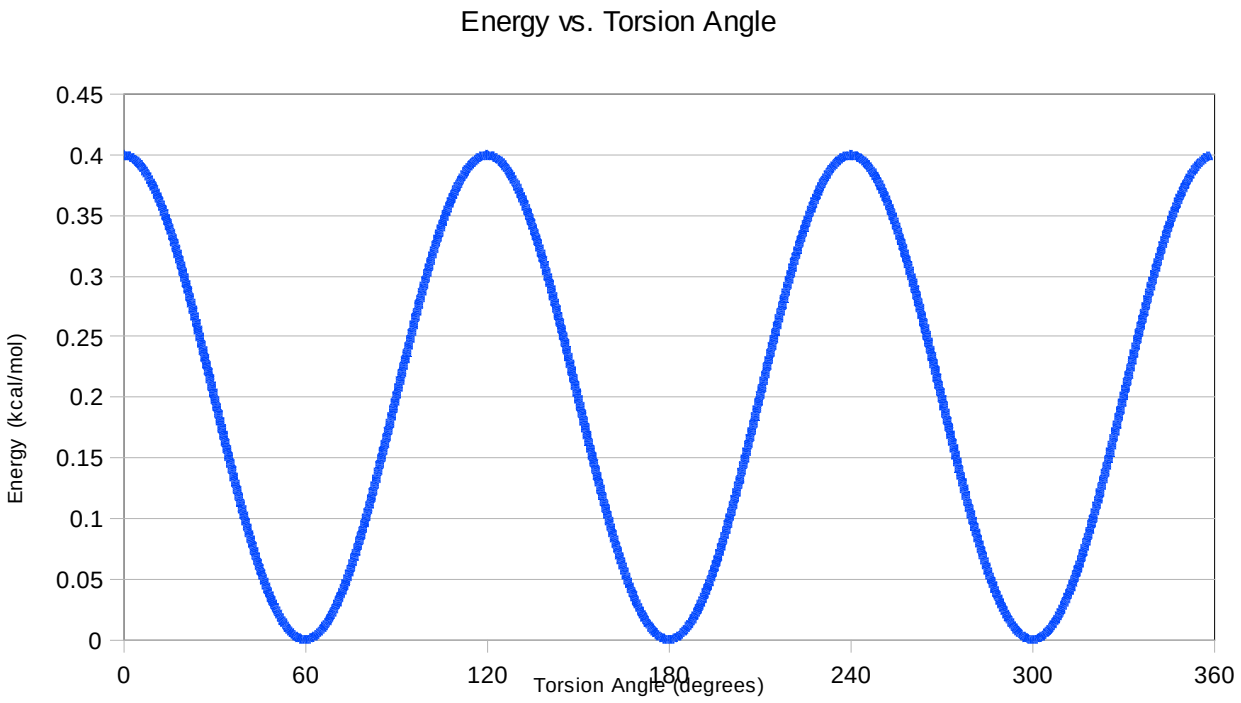
Reference energy

Peptoids in Rosetta: Energy Function Modifications

Torsions

Default CHARMM 27

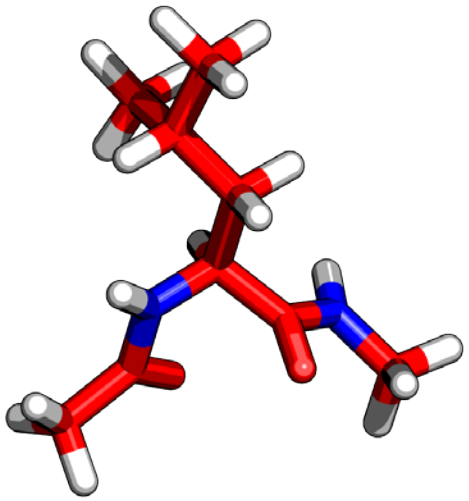
Need new parameters for peptoid nitrogen



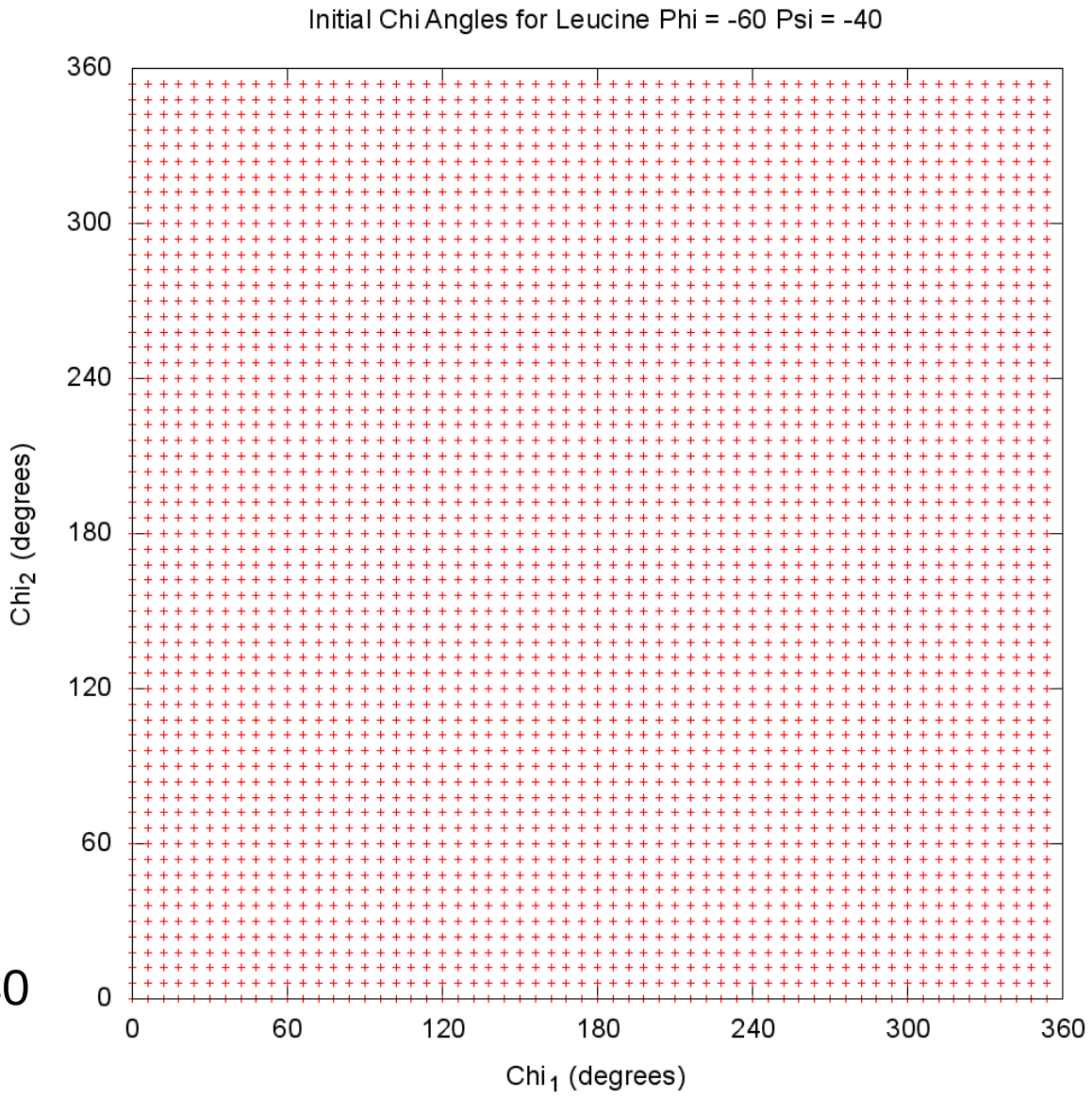
Peptoids in Rosetta: Rotamer Libraries

dipeptide models

- span torsion space



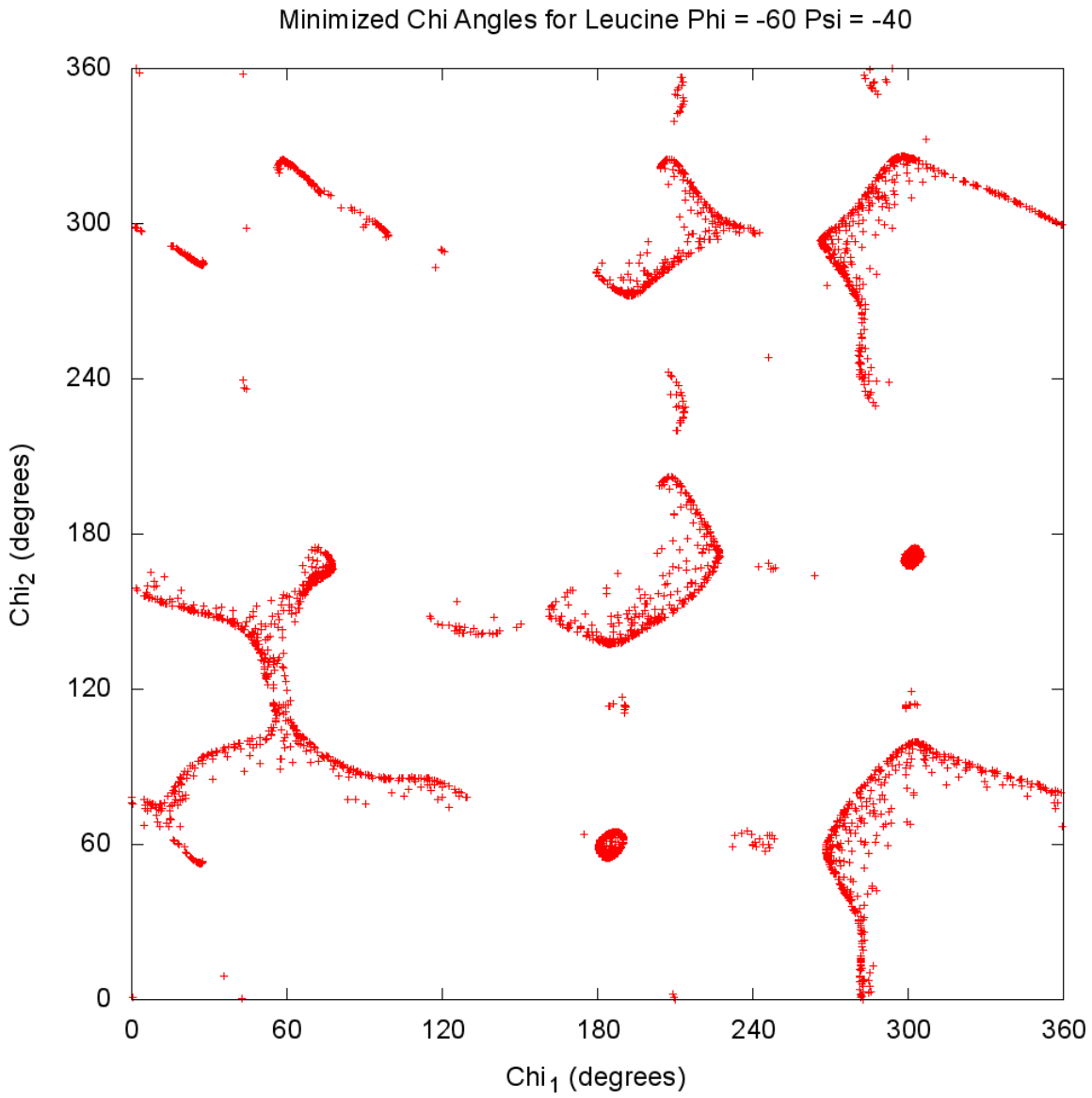
Leucine phi=-60, psi = 40



Peptoids in Rosetta: Rotamer Libraries

Minimize side chains

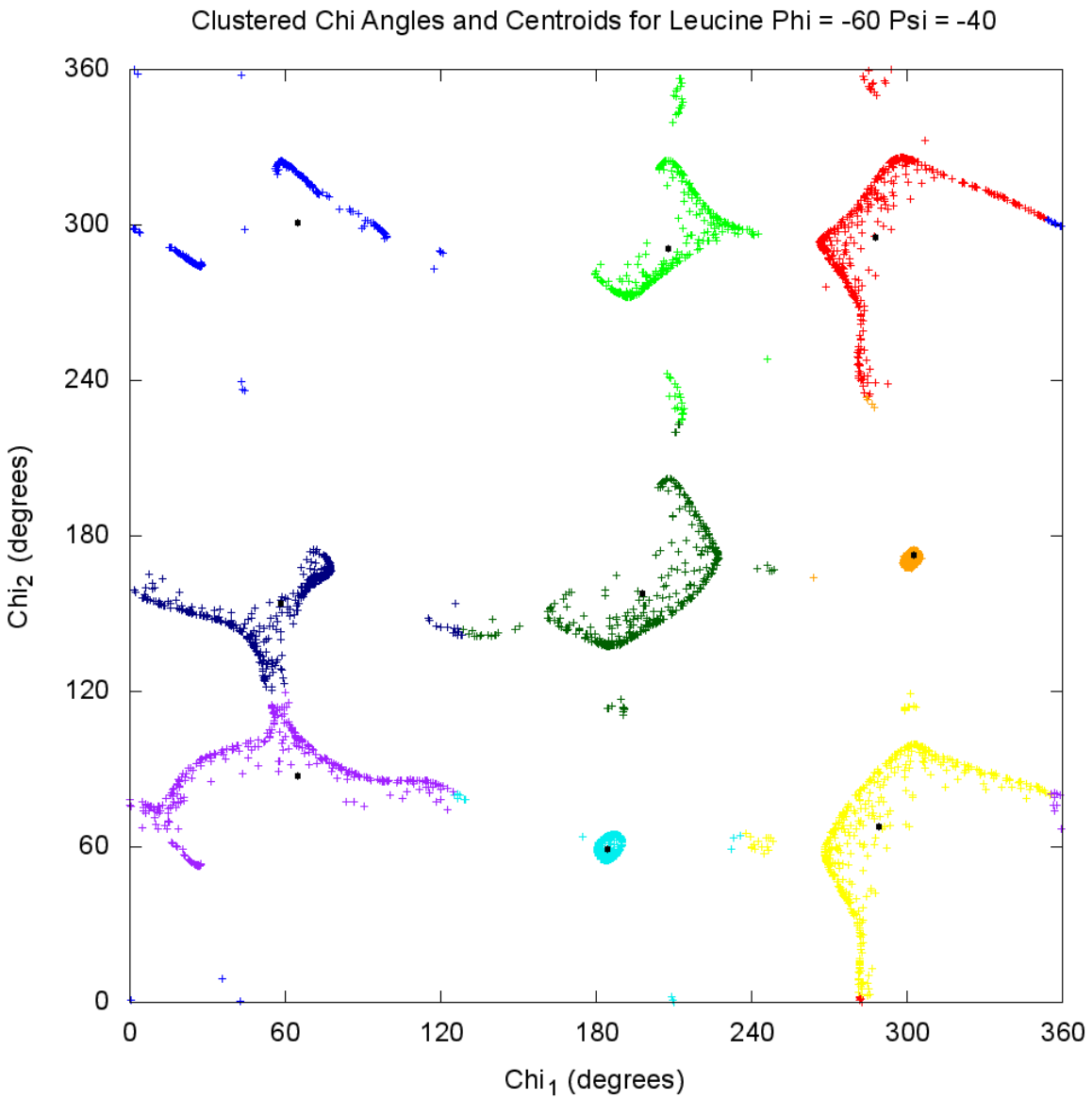
Backbone dihedrals fixed



Peptoids in Rosetta: Rotamer Libraries

Cluster χ angles

Low energy side chains form compact clusters

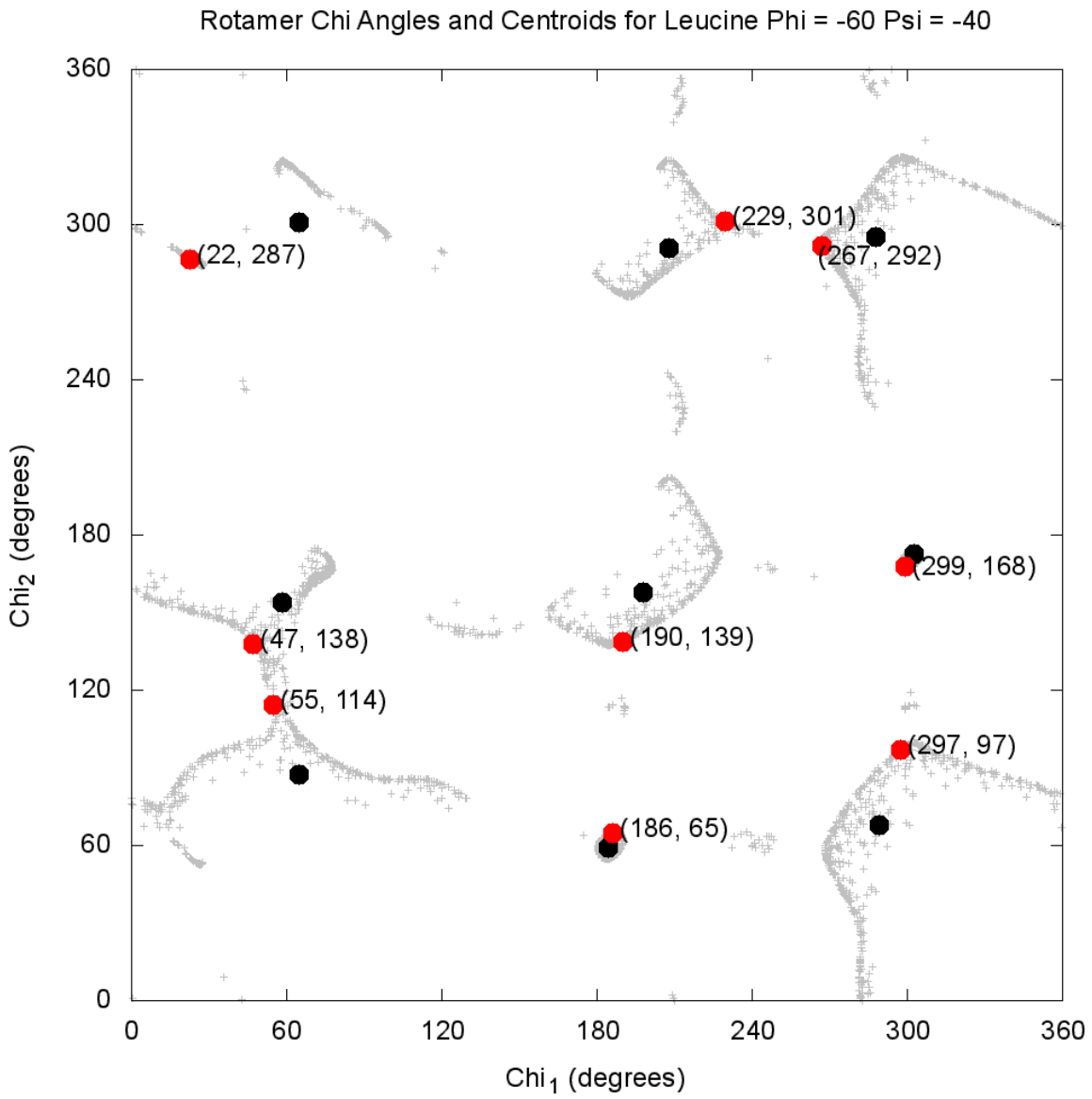


Peptoids in Rosetta: Rotamer Libraries

Each cluster represents a rotamer

Angles from lowest Energy side chain

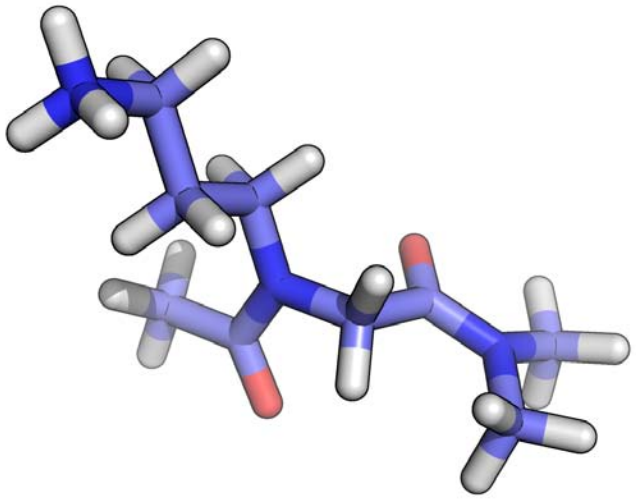
Energies converted To probabilities



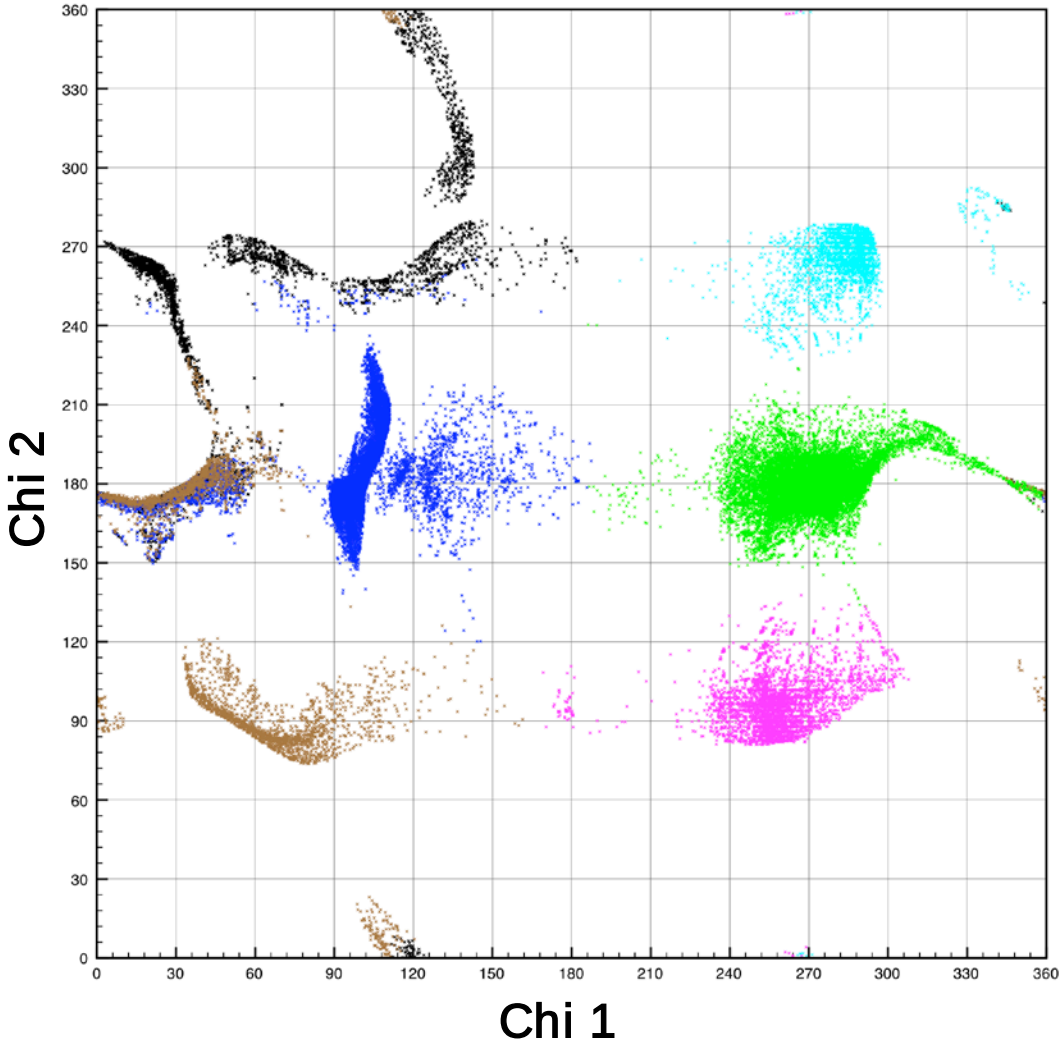
Rotamer

Cluster center

Peptoids in Rosetta: Rotamer Libraries

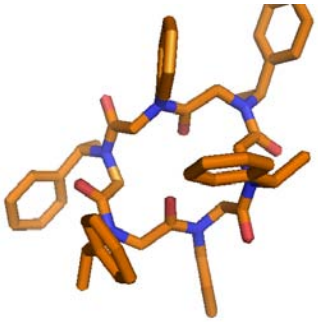


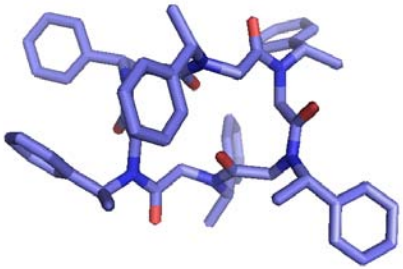
Ornithine-like peptoid



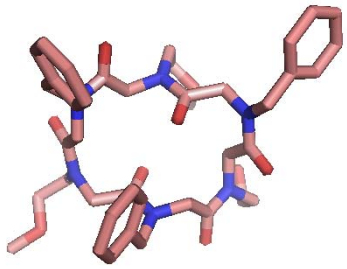
Peptoids: examples

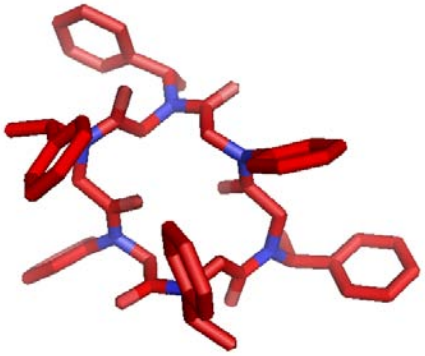
Cyclo-hexamers with same backbone structure





QuickTime™ and a
decompressor
are needed to see this picture.



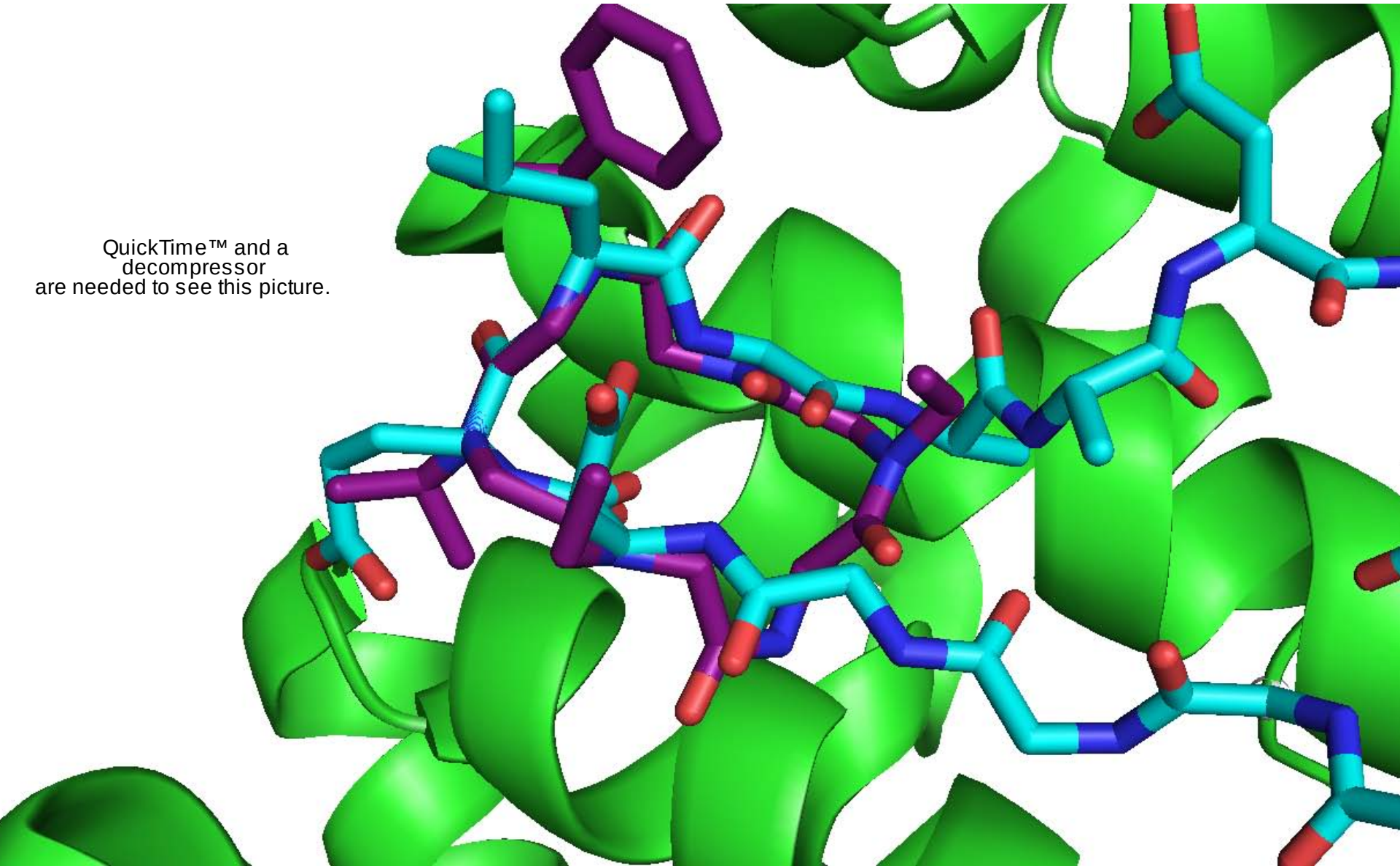


Blue: cyclic hexamer

Yellow: peptide type-I β-turn

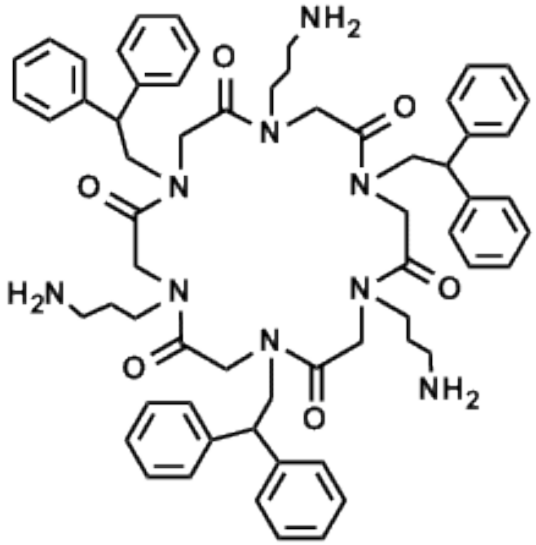
Purple: Peptoid macrocycle
Cyan: TCF
Green: β-Catenin

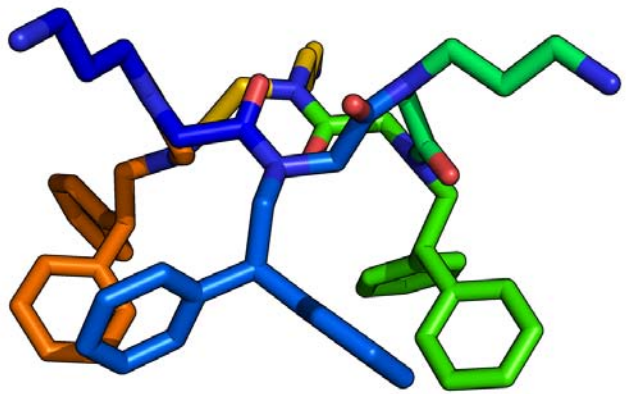
QuickTime™ and a
decompressor
are needed to see this picture.

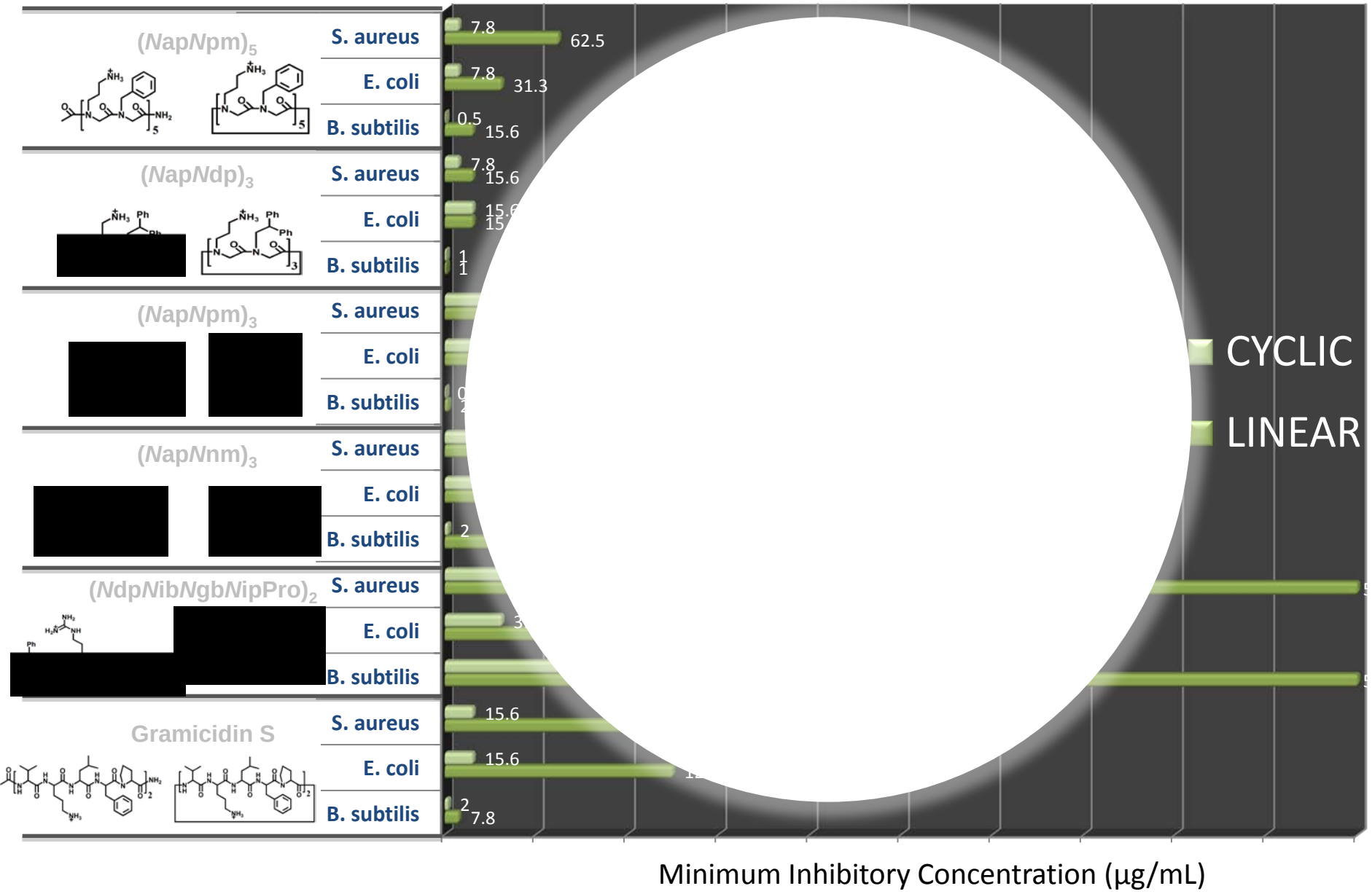


Peptoids: examples

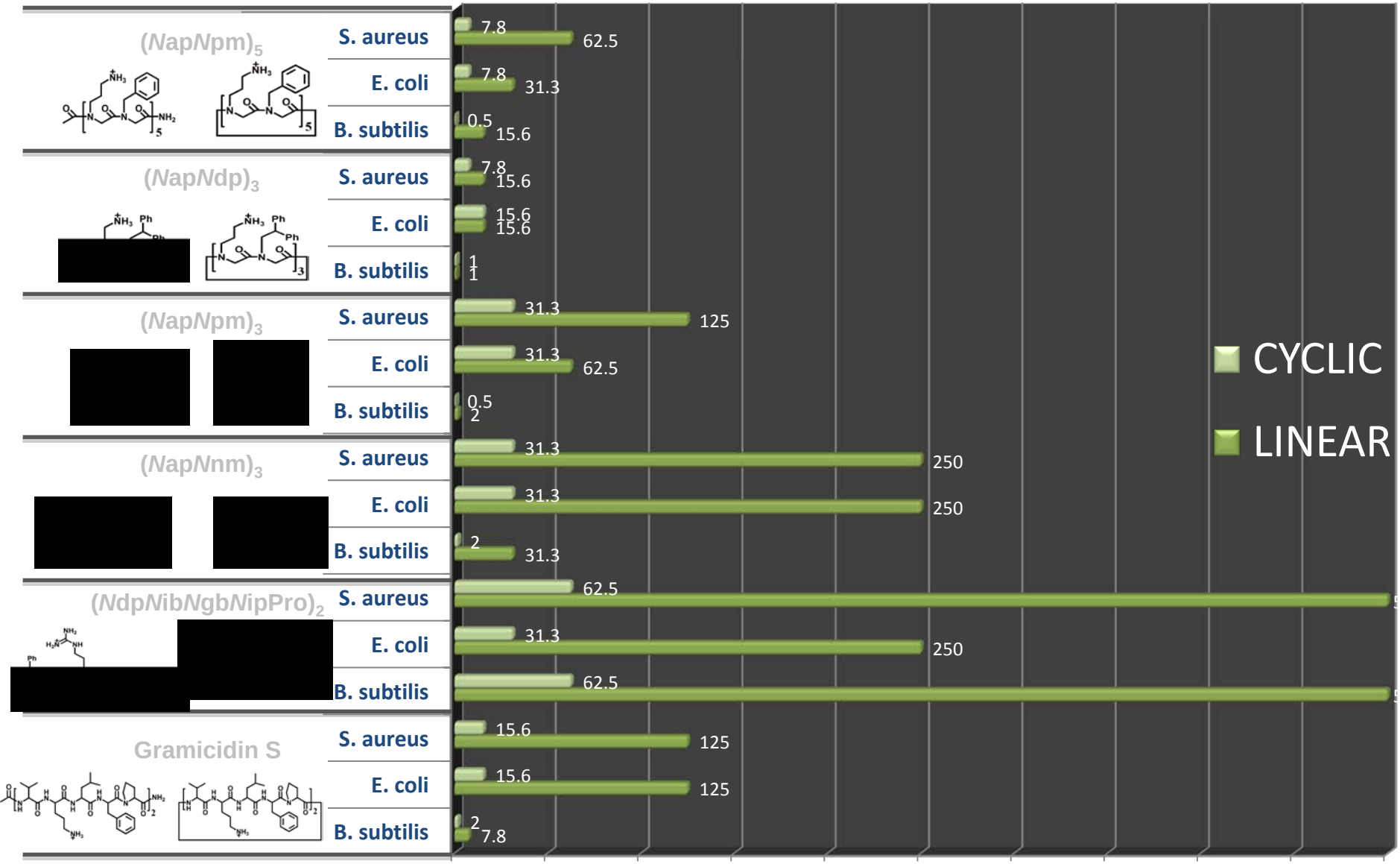
Peptoid cyclo-hexamers as broad spectrum antibiotics







Slide: Mia Huang

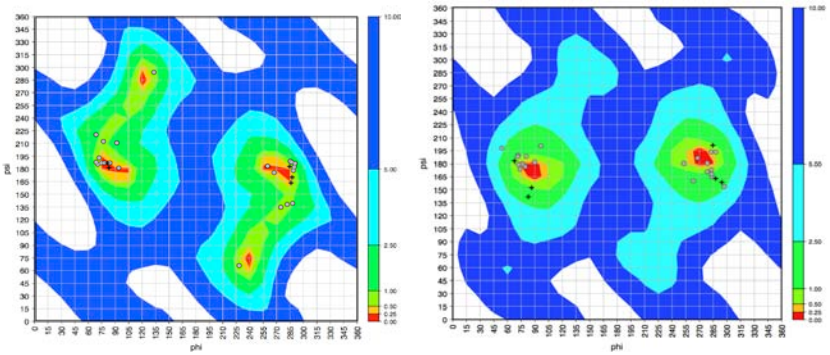


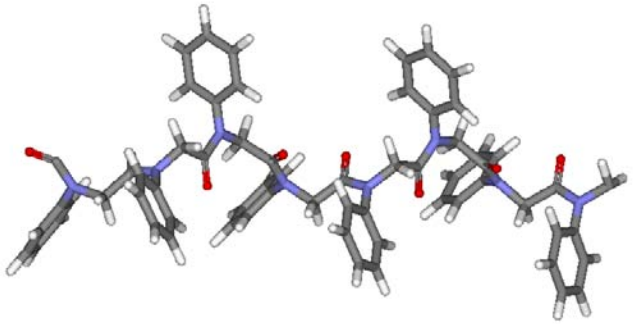
Slide: Mia Huang

Conclusions

Peptoid backbones are well predicted by theoretical models

— likely a good platform for design

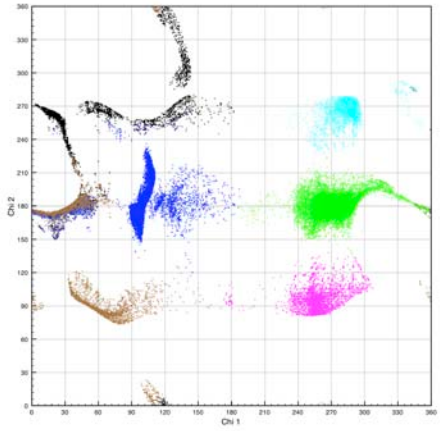




We are beginning to understand preferences of various peptoid residue types

— building blocks for rational design

We are developing tools to model peptoids in Rosetta



Rich Bonneau

Doug Renfrew

Kent Kirshenbaum

Mia Huang

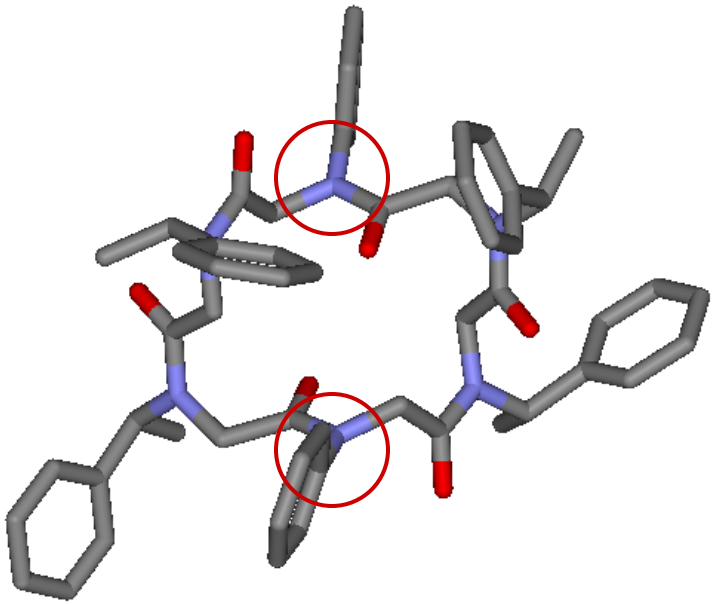
Neel Shah

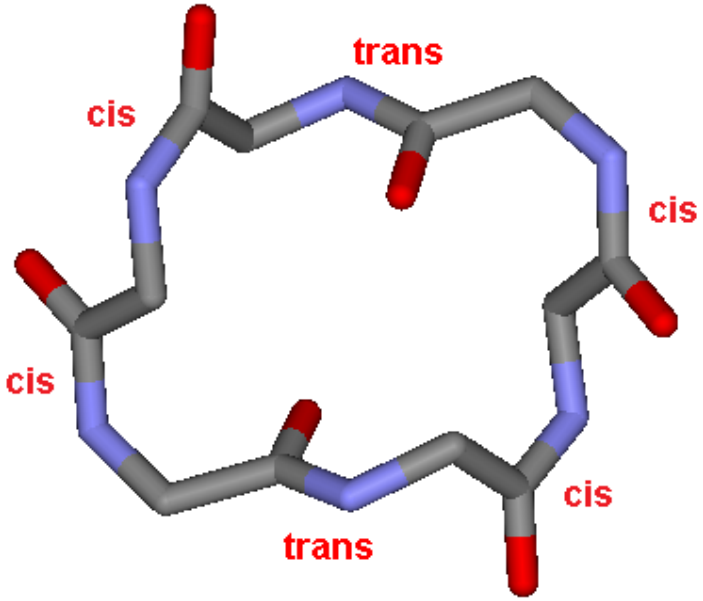
Peptoids: *N*-aryl side chains

Cyclic Scaffold Bearing *N*-aryl Side Chains

N-aryl at residues at *i* and *i* + 3:

crystal structure shows a predicted structure



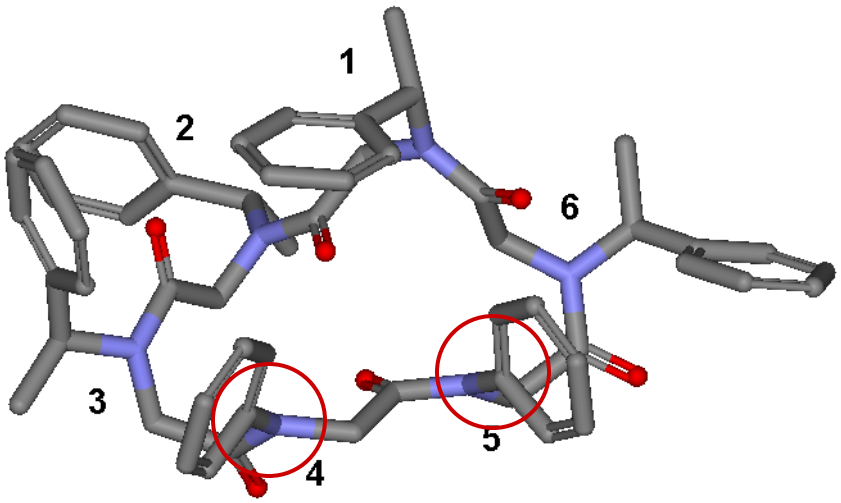


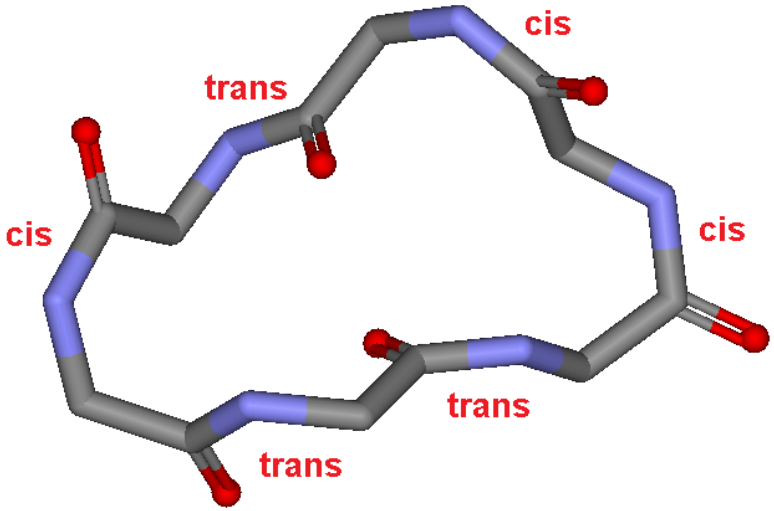
Peptoids: *N*-aryl side chains

Cyclic Scaffold Bearing *N*-aryl Side Chains

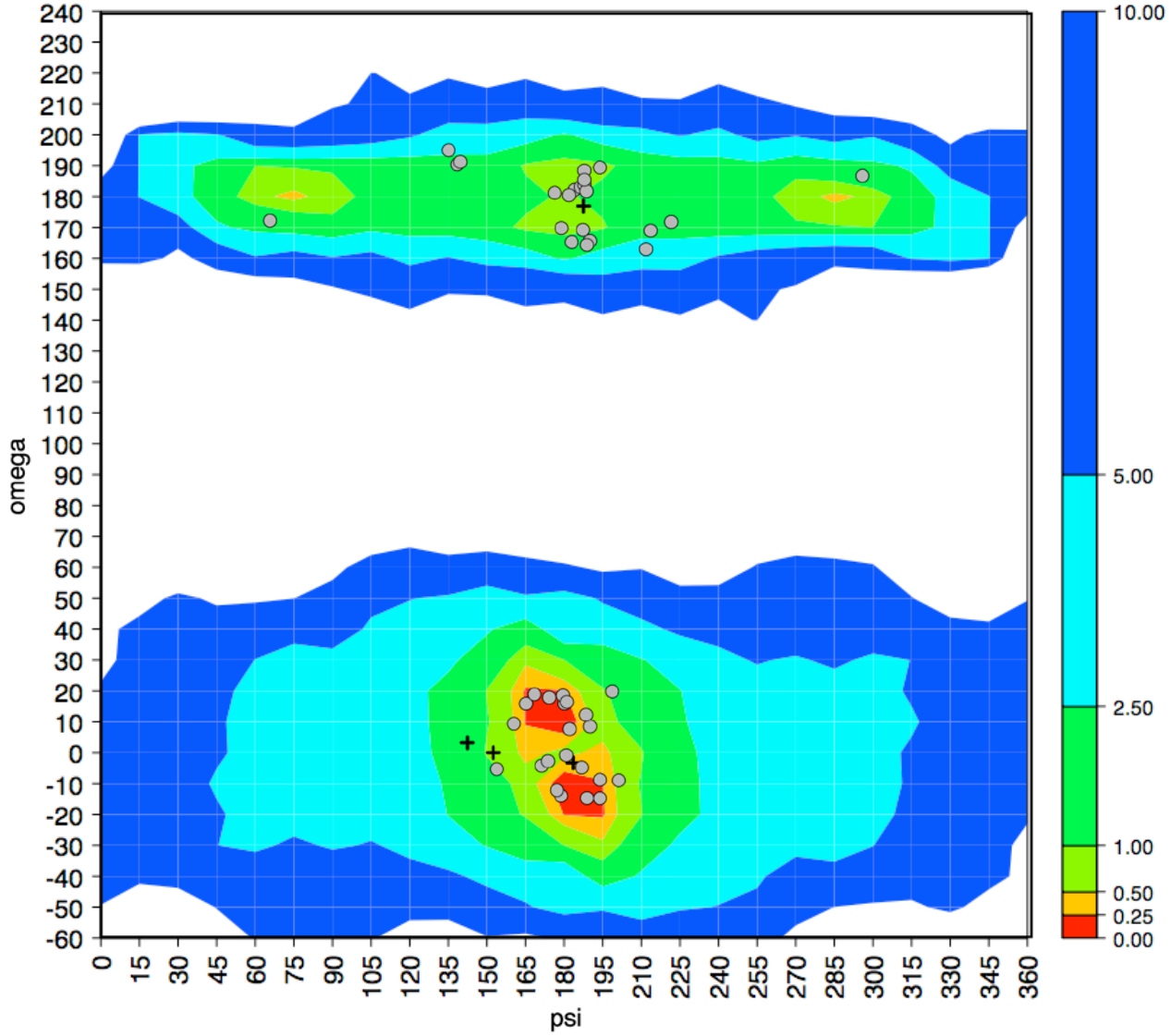
N-aryl at residues at *i* and *i* + 1:

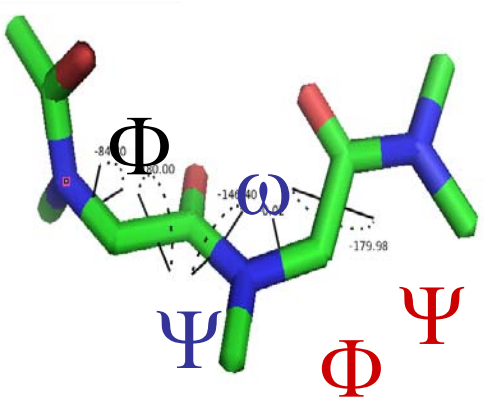
model structure based on HSQC, COSY, and NOE:





Peptoids: psi vs omega





Peptoids: phi vs omega