Macrocyclic Peptides as Ligands for Cellular Receptors. When a little rigidity is just right.....

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G protein-coupled receptors

- 60% of all drugs target GPCR's
- Mostly biogenic amines
  - Dopamine
  - $5HT_{1-7}$
  - Histamine
- Few peptide-binding GPCR's successfully targeted
  - Somatostatin
  - Angiotensin
- Why?

Complement Factor 5a and Inflammatory Disease

C5a binds to :

neutrophils
monocytes
macrophages
T lymphocytes
mast cells
glial cells
neurones
vascular endothelial cells

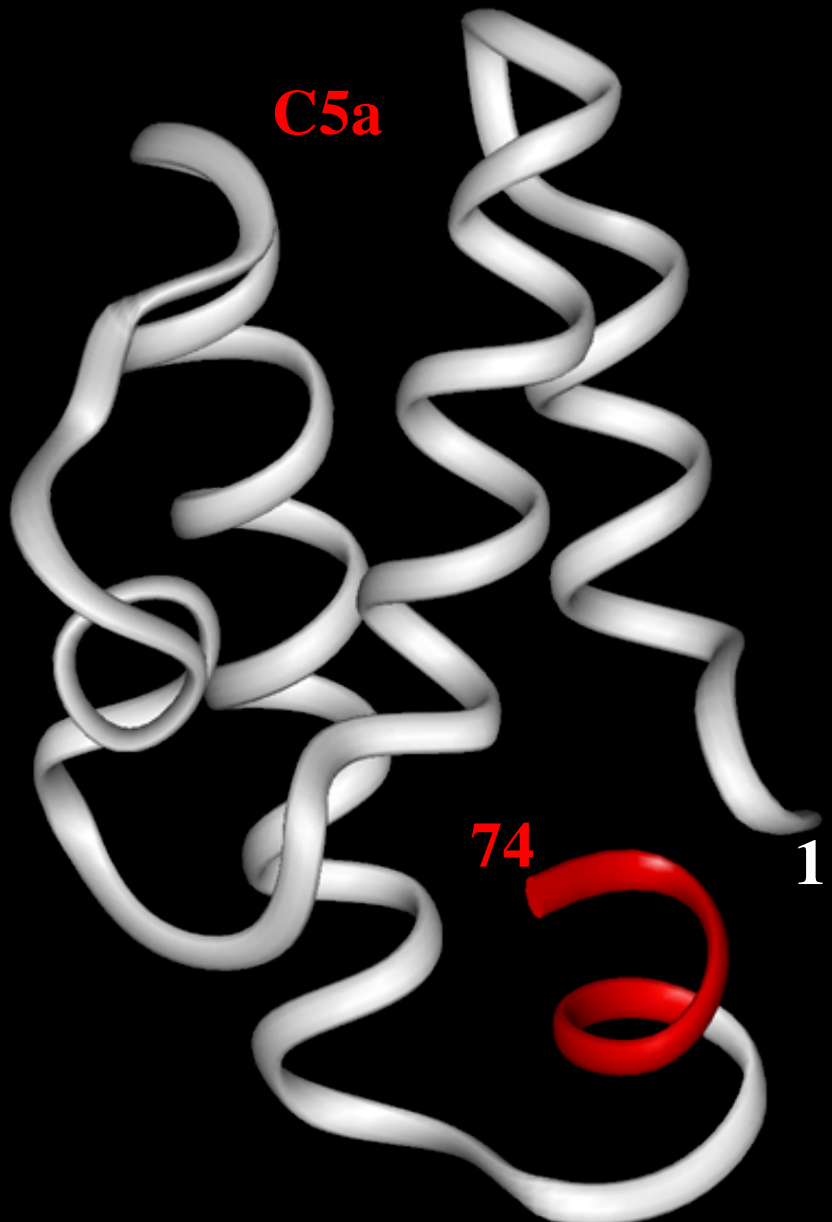
C5a causes :

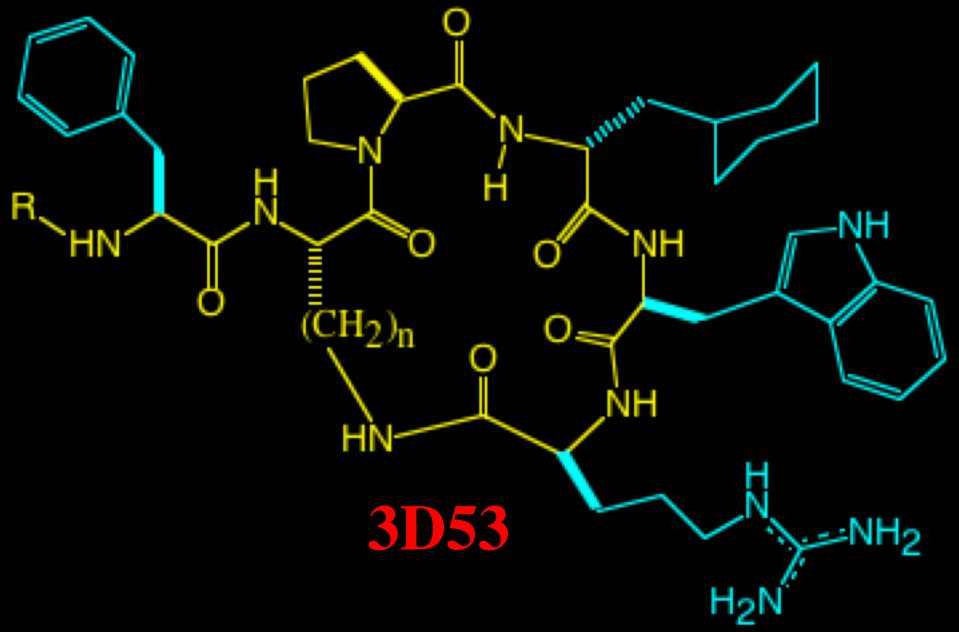
muscle contraction
vascular leakage
chemotaxis
neutrophil/endothelial adhesion
release of cytokines-TNFα, IL-1
T-lymphocyte proliferation
IgG production

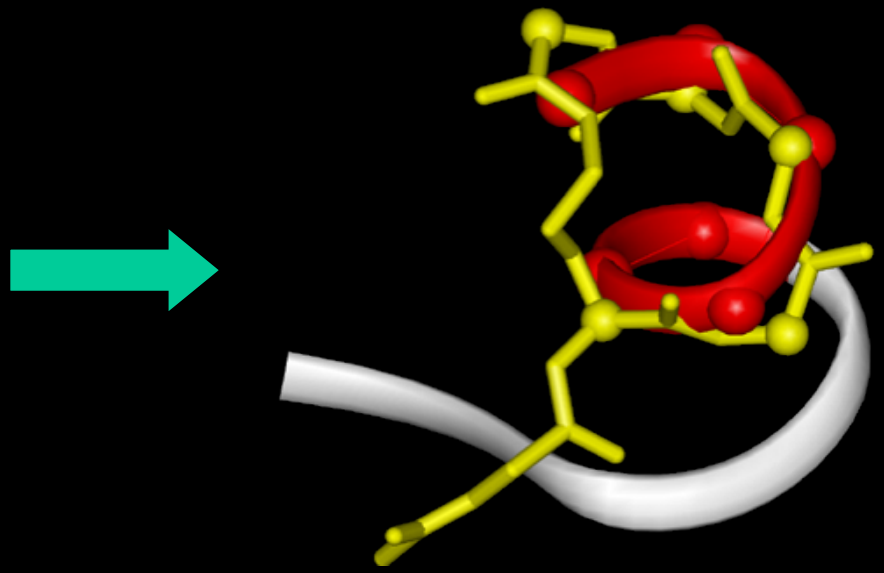
Conditions :

Rheumatoid arthritis
Sepsis
ARDS
Crohn's disease
Ischemic disease
Reperfusion injury
Myocardial infarct
Pancreatitis
Allergy
Psoriasis
Lupus
Diabetes type I
Fibrosis
Alzheimer's disease
Multiple sclerosis

Antagonist Mimics Helical Turn of C5a







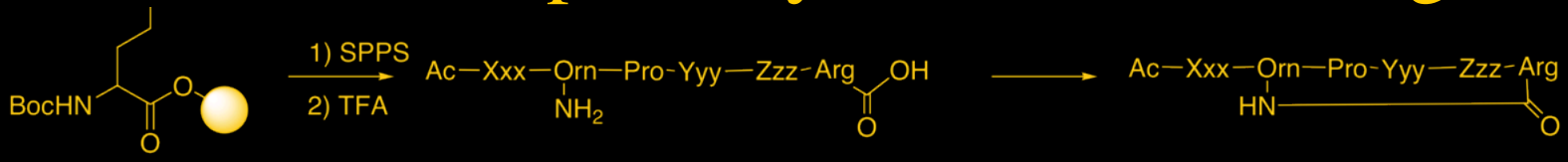
Aims

- Synthesis and testing of analogues
- NMR structures of 3D53 and analogues
  - Macrocycle shape
  - Side chain locations (α–β, β–γ vectors)
- Develop SAR of C5a antagonism

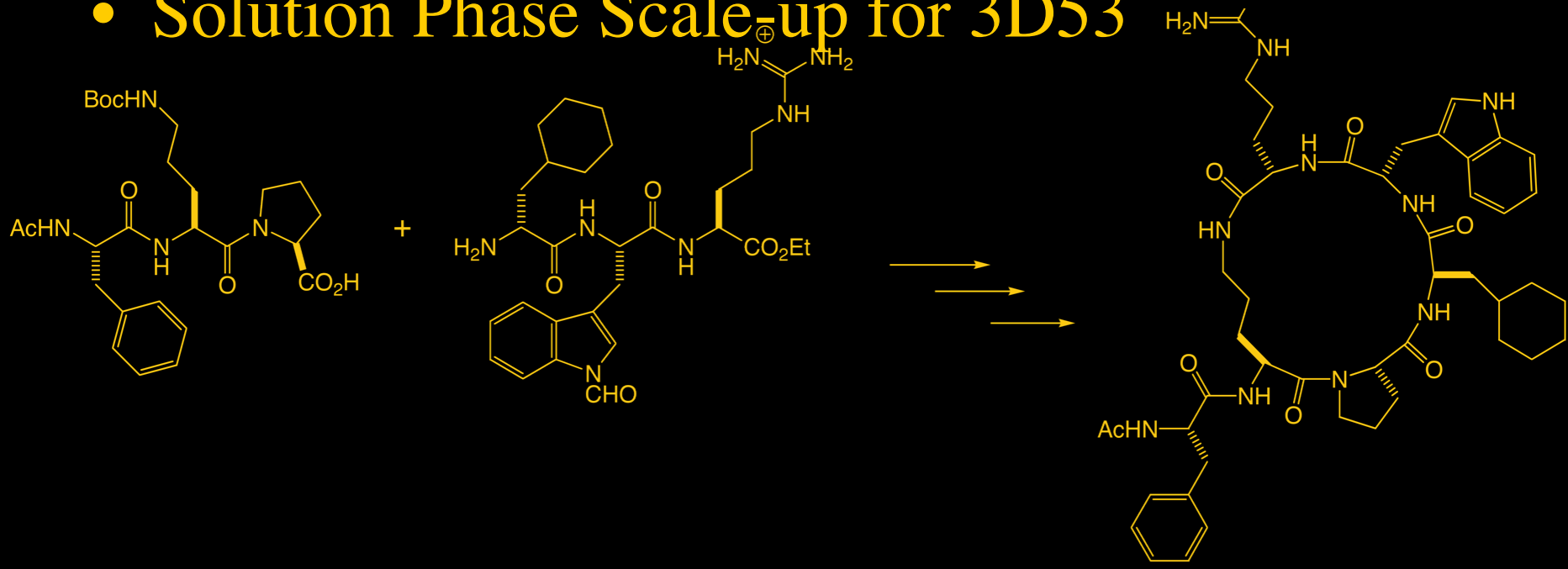
- Pharmacophore Development

Synthesis

- Solid Phase Peptide Synthesis for Analogues

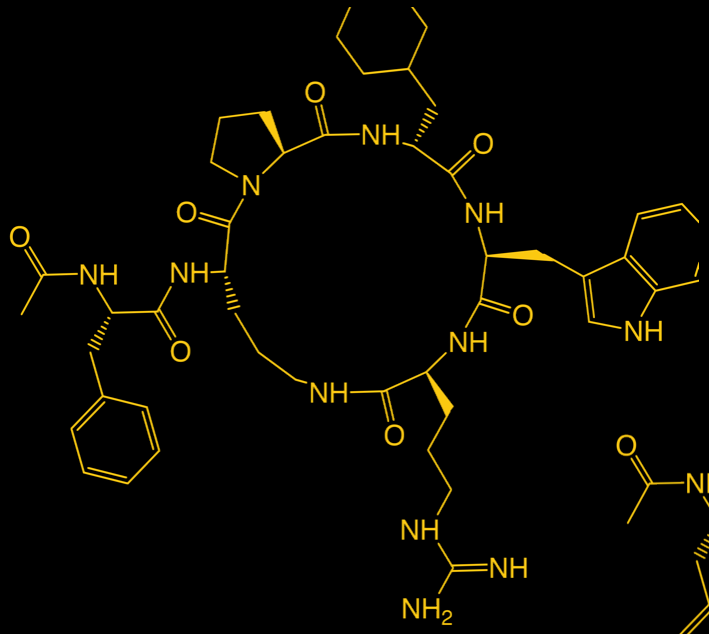


- Solution Phase Scale-up for 3D53

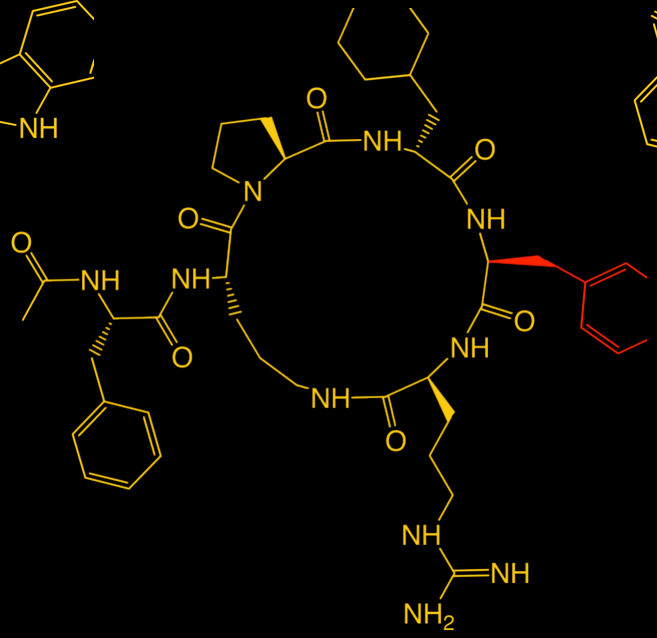


- R.C. Reid, G. Abbenante, S.M. Taylor, and D.P. Fairlie*; J. Org. Chem.*; **2003;** *68*, pp 4464 - 4471

NMR studies of 3D53 analogues



3D53



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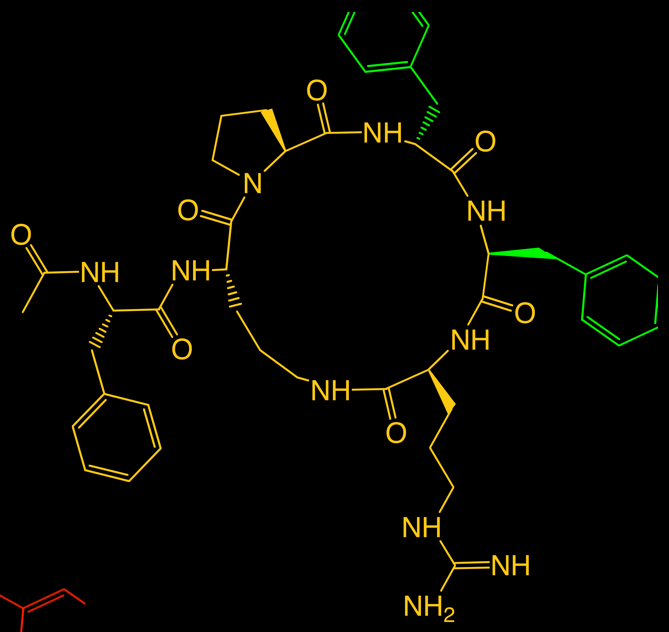

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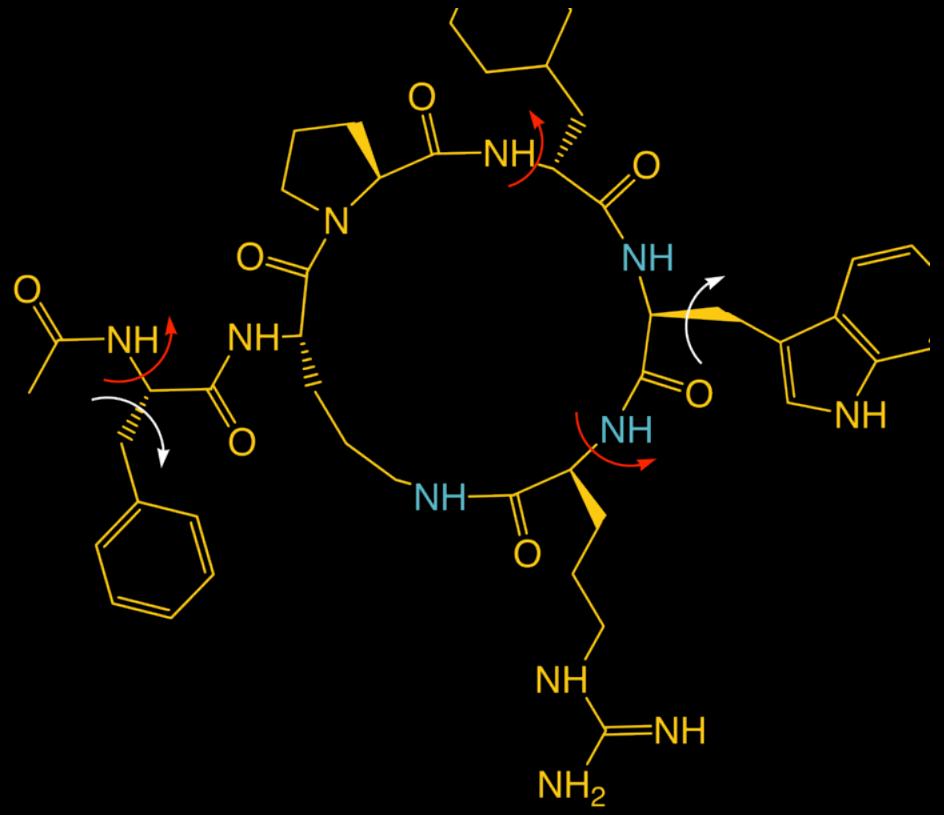
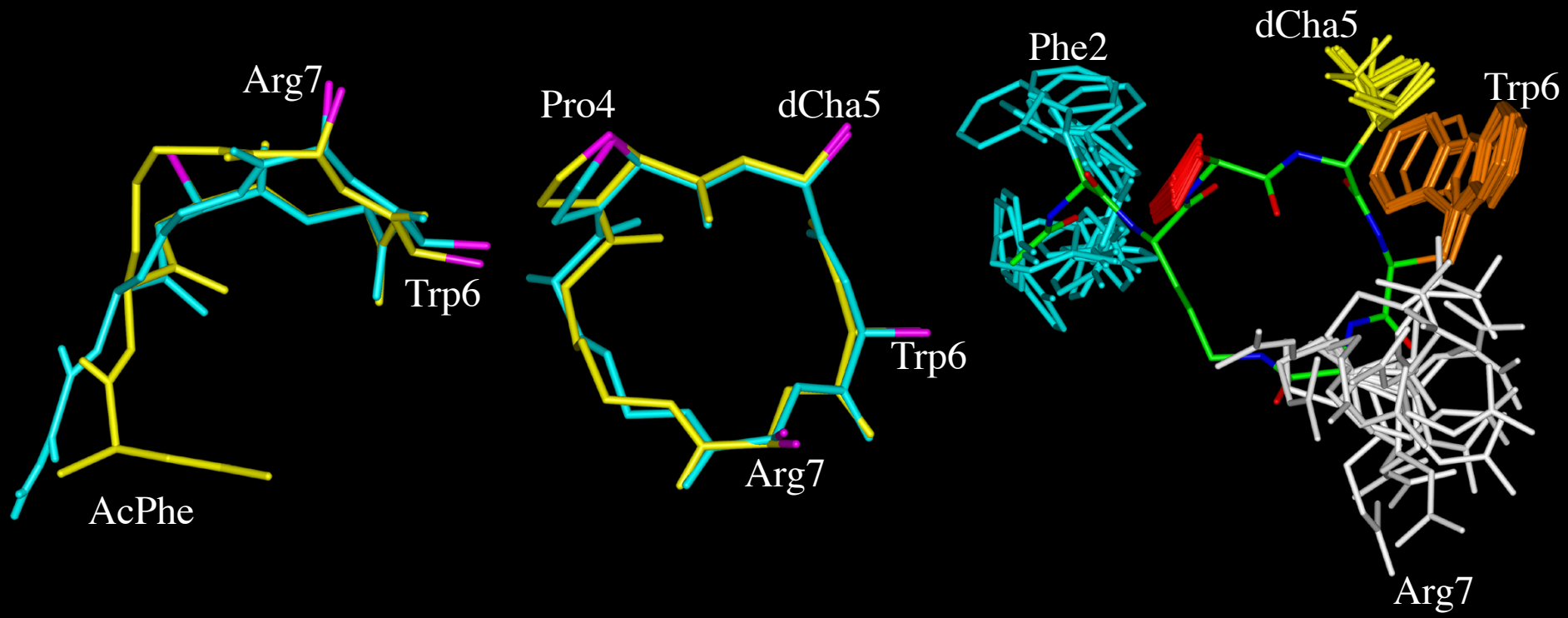
3D53 NMR data

- 129 NOE's
- 3 ϕ restraints
- 2 χ_1 restraints
- VT NMR
- D_2O exchange



3D53 NMR structure



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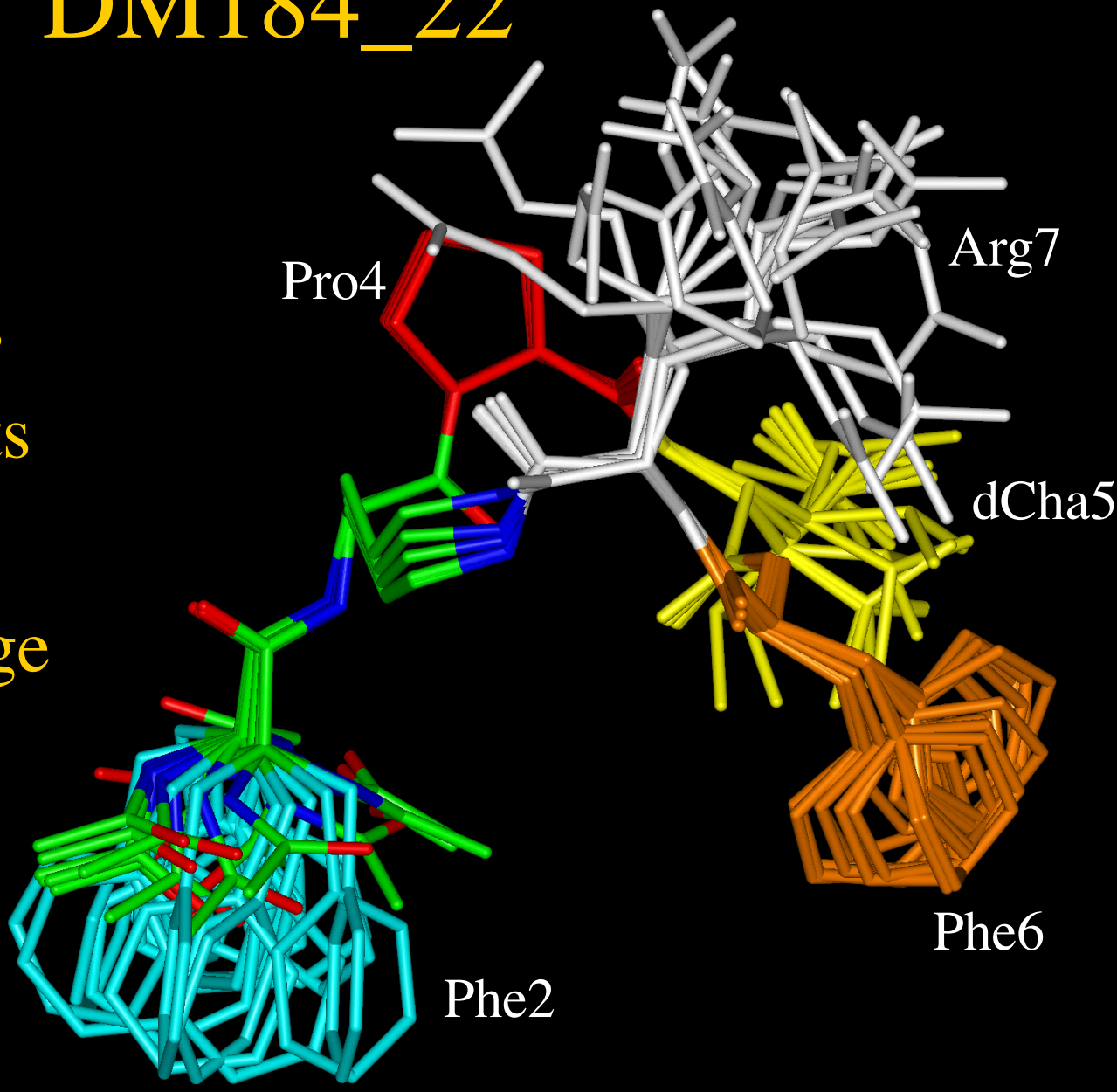
- 79 NOE's
- 3 ϕ restraints
- 2 χ_1 restraints
- VT NMR
- D_2O exchange



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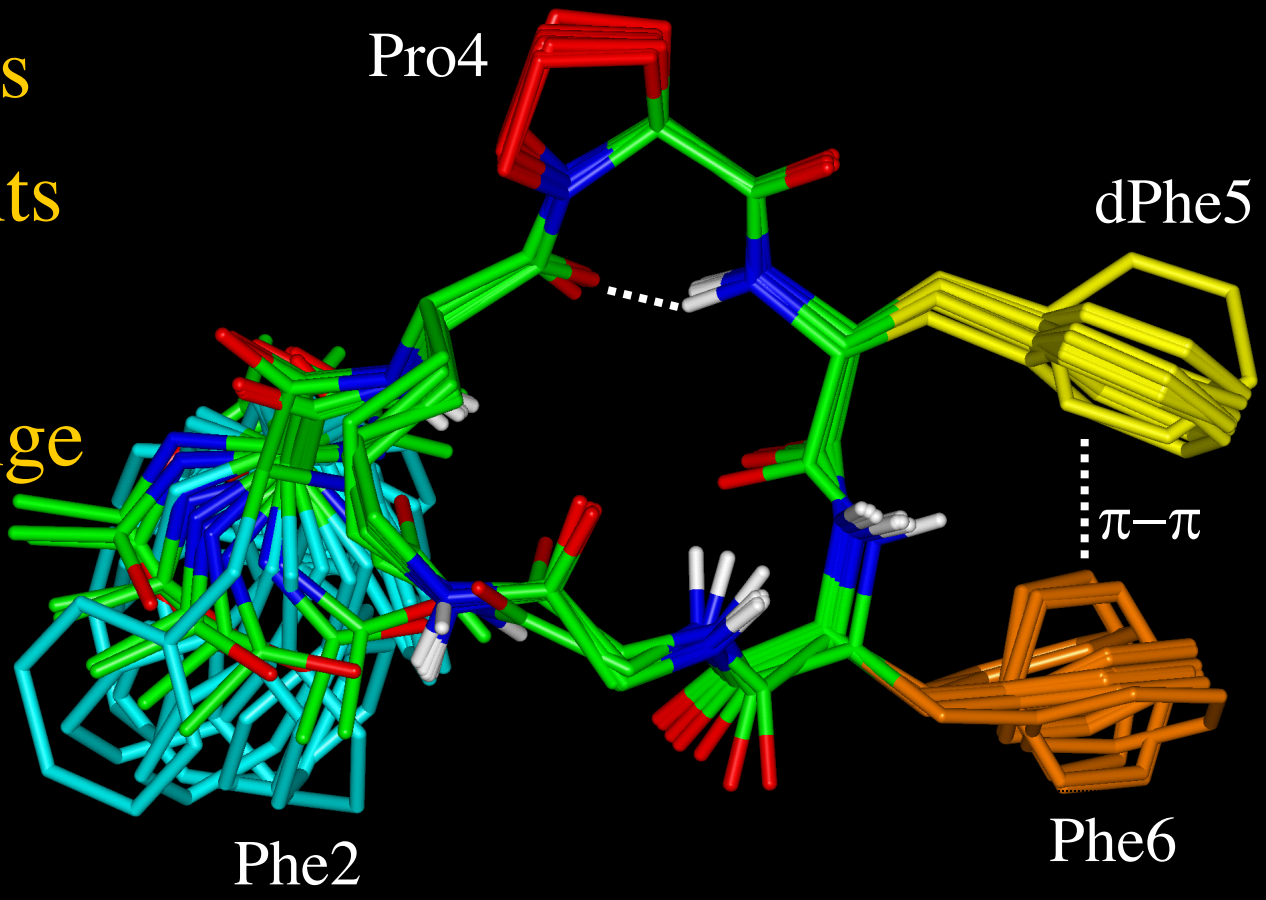
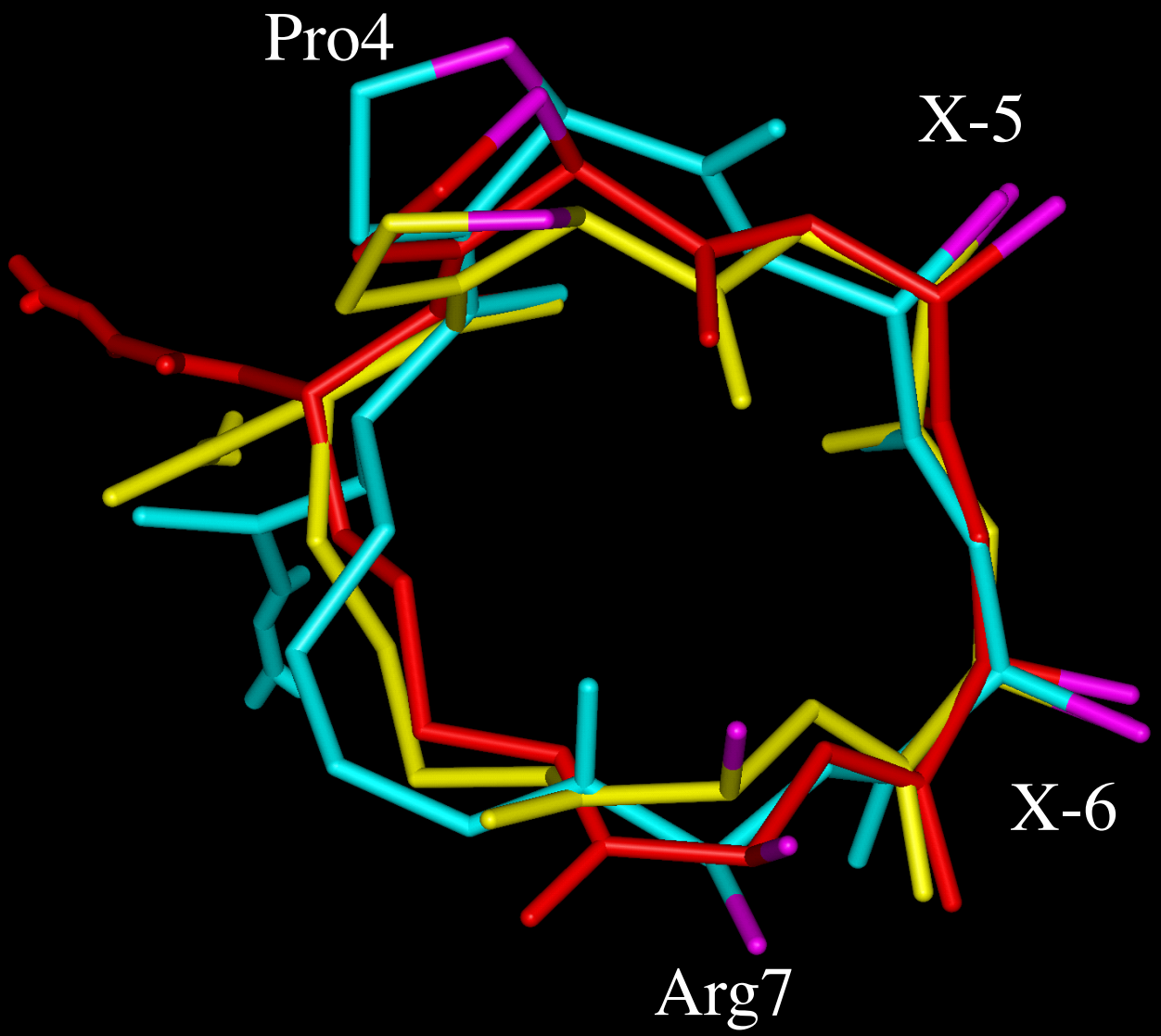


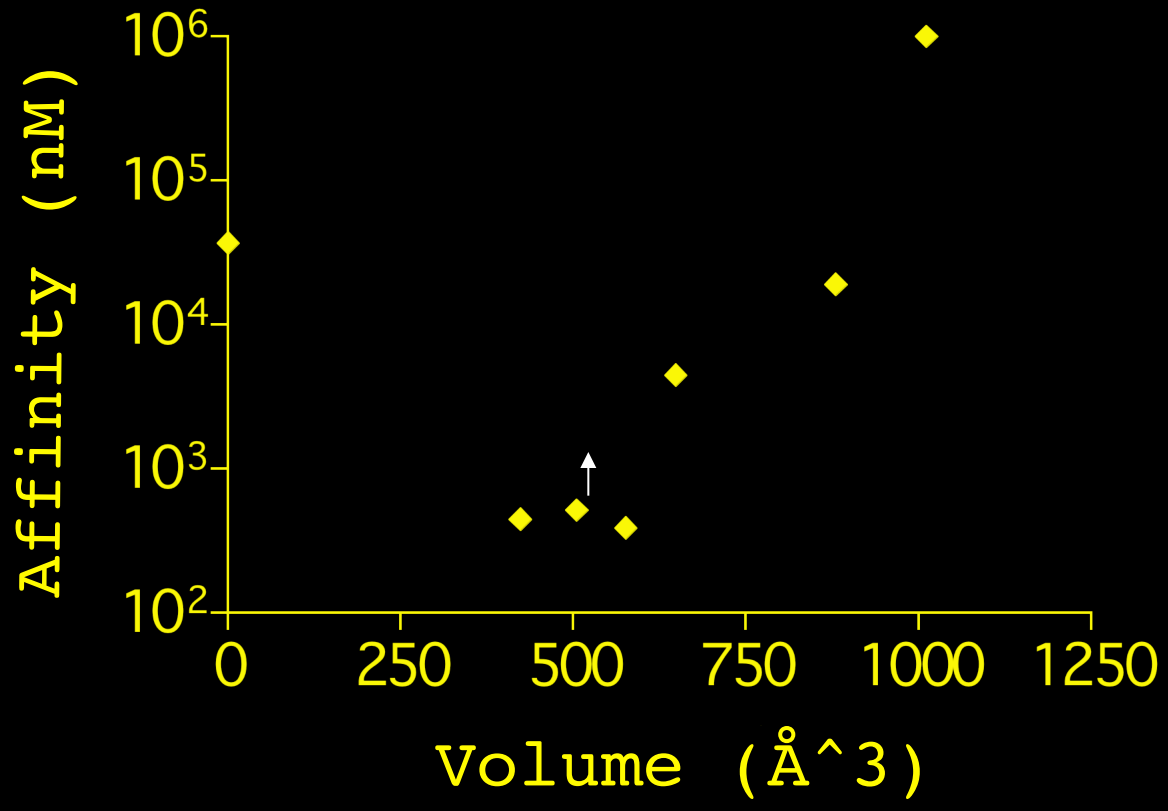
NMR overlay

- α-β vectors
- β-γ vectors
- Scaffold shape



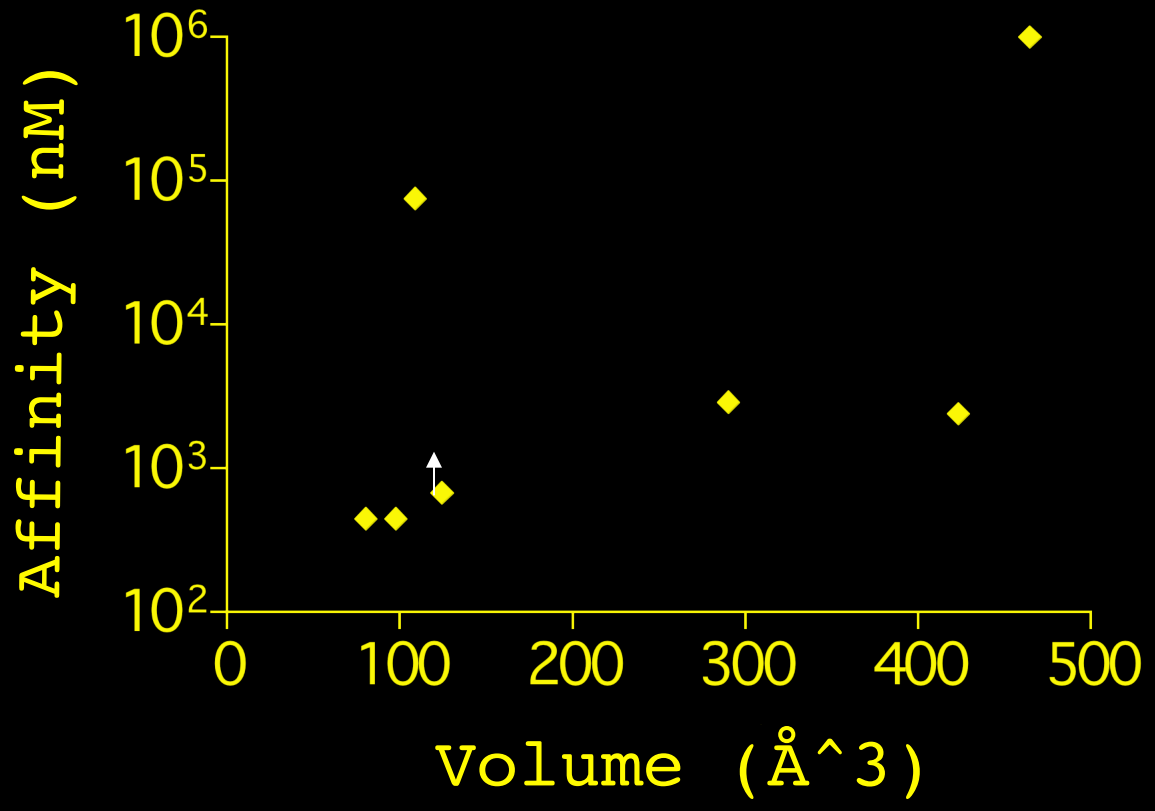
SAR - 1: Phe replacements

- Gly
- Phe
- (*o*-F)Phe
- (*m*-F)Phe
- Tyr
- Trp
- hPhe



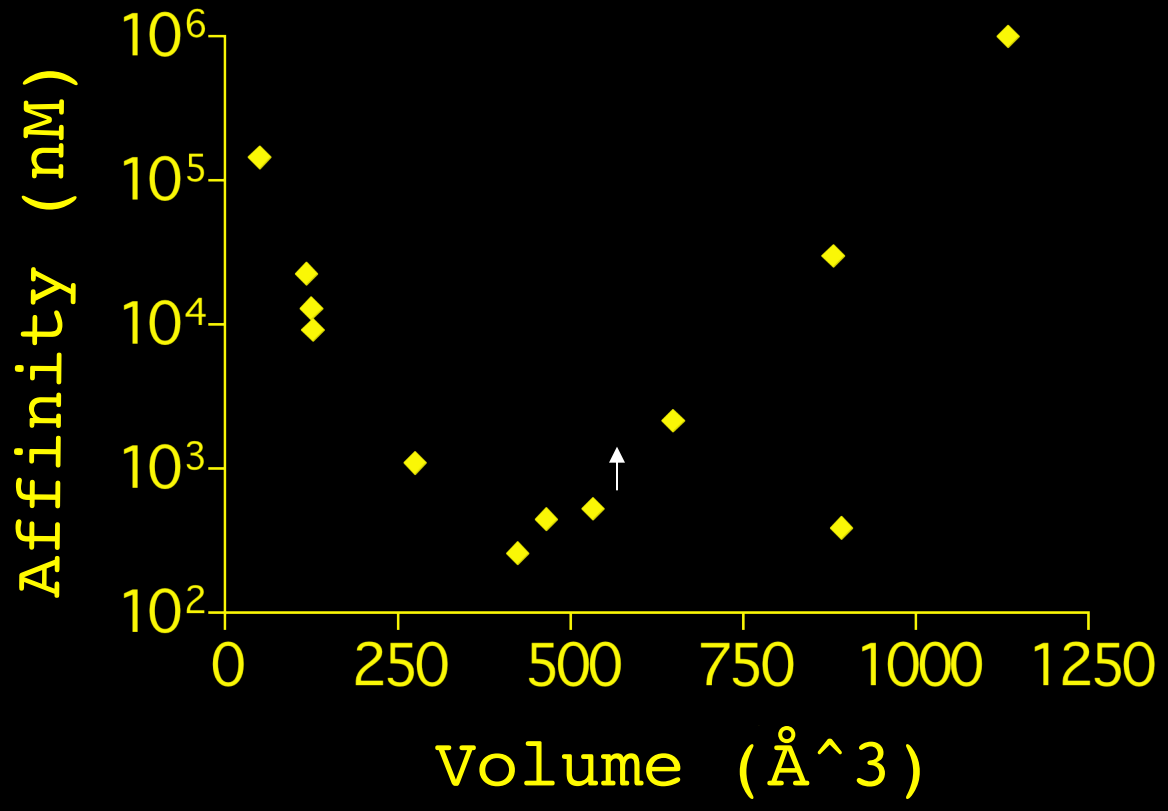
SAR - 2: Pro replacements

- Pro
- Hyp
- ThiaPro
- Val
- Ile
- Phe
- Cha



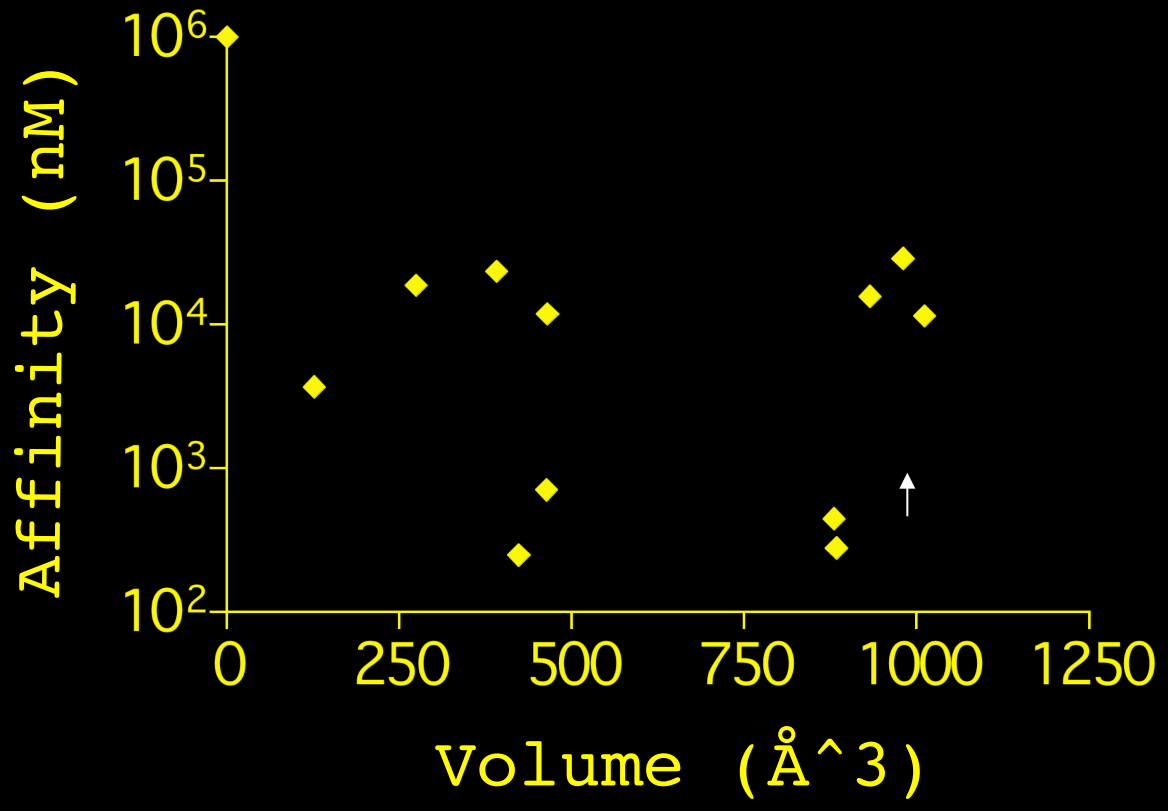
SAR - 3: D-Cha replacements

- D-Ala
- D-Aic
- D-Val
- D-Tic
- D-Leu
- D-Phe
- D-Cha
- D-Nle
- D-Tyr
- D-Trp
- D-hCha
- D-Arg



SAR - 4: Trp replacements

- Gly
- Tic
- Leu
- His
- Phe
- 1-Nal
- Cha
- Trp
- Bta
- 2-Nal
- Fla
- hPhe



Summary

- NMR studies
  - Macrocycle is moderately flexible
  - Side chain positions independent of macrocycle shape
  - Side chains key determinants of activity
- Pharmacophore Development
  - 3 Hydrophobic residues on one face of macrocycle
  - Bulky (Trp) residue key determinant of antagonism
  - Arginine residue projected away from other binding residues

Acknowledgments

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  - David Fairlie
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courtesy Graham Meltzer Contemporary Photography