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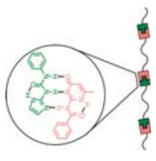
"Adventures in Non-Covalent Chemistry: From Self-Assembly to Protein Surface Recognition"

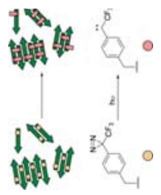
Andy Wilson e-mail: A.J.Wilson@leeds.ac.uk Ischia, IASOC 2014, 25th Sep

Self-assembled polymers



Soft Matter, **2007**, 3, 409-425, *Chem. Commun.* **2008**, 344-346, *Supramol. Chem.* **2008**, 21, 12-17, *Org. Lett.* **2011**, 13, 240-243, *Supramol. Chem.* **2011**, 23, 470-480, *OBC*, **2011**, 9, 5938-5940, *Chem. Eur. J.* **2011**, 17, 14508-14517, *Macromolecules*, **2012**, 45, 4723-4729, *OBC*, **2012**, 10, 4899-4906, *RSC Adv.*, **2013**, 3, 3103 – 3108, *Chem. Sci.*, **2013**, 4, 1825-1829, *Macromolecules*, **2013**, *46*, 9634–9641

Photocrosslinking applied to self-assembly



Chem. Commun. **2008**, 5728-5730
Anal. Chem. **2012**, 84, 6790–6797
Chem. Soc. Rev. **2013**, 42, 3289-3301
ACS Chem. Biol., **2014**, 9, 761–768

1

ASTBURY CENTRE

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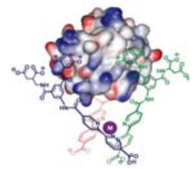
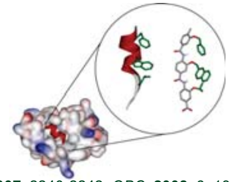
Protein-surface mimetics



Chem. Soc. Rev., **2009**, 38, 3289-3300
Chem. Eur. J. **2010**, 16, 100-103
Chem. Commun. **2011**, 559-561
Bioorg. Med. Chem. Lett., **2012**, 22, 985-988
Chem. Eur. J. **2012**, 18, 13733-13742
Org. Biomol. Chem., **2013**, 11, 2206-2212

'Foldamers' and Constrained Peptides as inhibitors of PPIs



Chem. Commun. **2007**, 2240-2242, *OBC*, **2008**, 6, 138-146, *Tetrahedron Lett.*, **2009**, 50, 2236-2238, *Chem. Commun.* **2009**, 5091-5093, *Chem. Soc. Rev.*, **2009**, 38, 3289-3300, *Tetrahedron Lett.*, **2010**, 51, 1361-1363, *OBC*, **2010**, 8, 2344-2351, *Amino Acids*, **2011**, 41, 743-754, *Tetrahedron*, **2012**, 68, 4485-4491, *OBC*, **2012**, 10, 6469-6472, *PLoS ONE*, **2012**, 7, e43253, *Bioorg. Med. Chem.* **2013**, 21, 4034-4040, *Nature Chem.*, **2013**, 5, 161-173, *Chem. Eur. J.*, **2013**, 19, 5546-5550, *EurJOC*, **2013**, 17, 3504-3512. *Chem. Commun.*, **2013**, *49*, 9131-9133. *Synlett*, **2014**, *25*, 324-335, *ChemBioChem*, **2014**, 15, 1083-1087.

2

Making Polymers Using Non-Covalent Links

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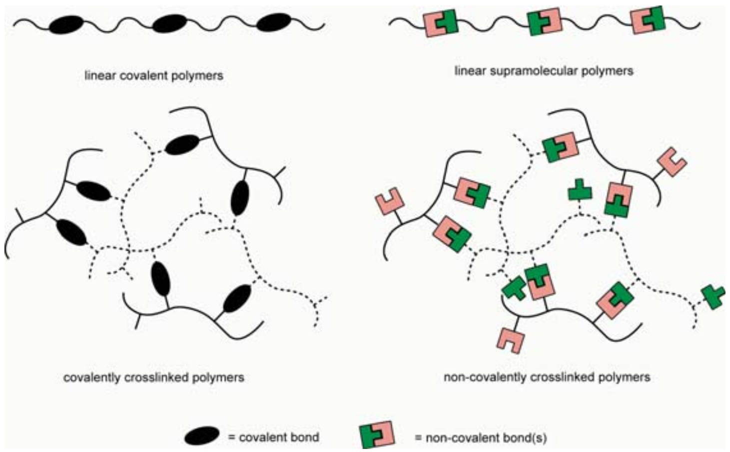

T. Aida, E. W. Meijer and S. I. Stupp, *Science*, **2012**, *335*, 813-817, J. D. Fox and S. J. Rowan, *Macromolecules*, **2009**, *42*, 6823-6835.

3

What Affects Association Constant?

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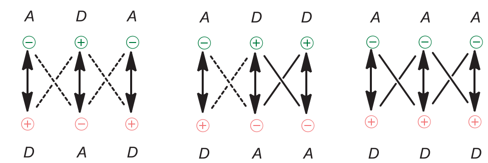
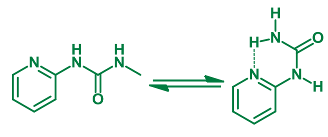


J. Sartorius and H.-J. Schneider, *Chem.-Eur. J.* **1996**, *2*, 1446-1452.
W. L. Jorgensen and J. Pranta, *J. Am. Chem. Soc.* **1990**, *112*, 2008-2010.

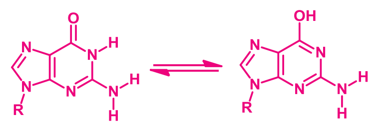
primary interaction = 1.9 Kcal
secondary interaction = ±0.69 Kcal

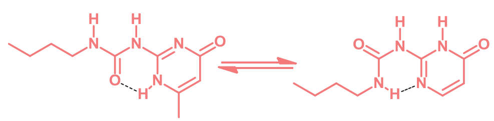
For DDA-AAD = 5.7 Kcal
K_a = 1 x 10^5 M^{-1}

For DDAA-DDAA = 9.0 Kcal
K_a = 3 x 10^7 M^{-1}



intra v intermoelcular H- bonds





tautomerism/ prototropy

4

Conformer Independent Arrays of Hydrogen-Bonds

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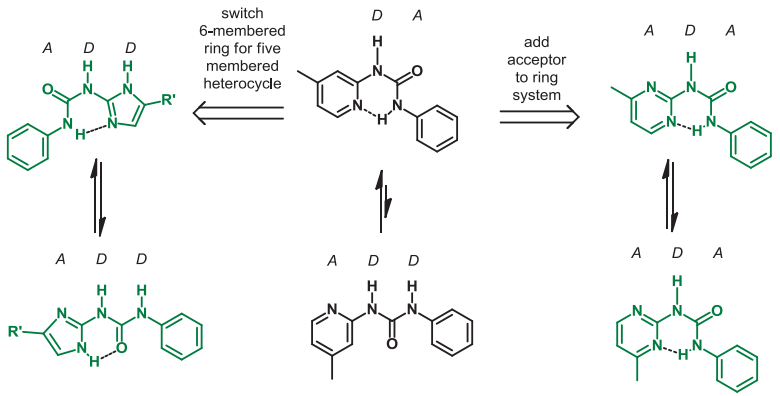

Electronic Substituent Effects upon Binding for ADD-DAA Heterodimer

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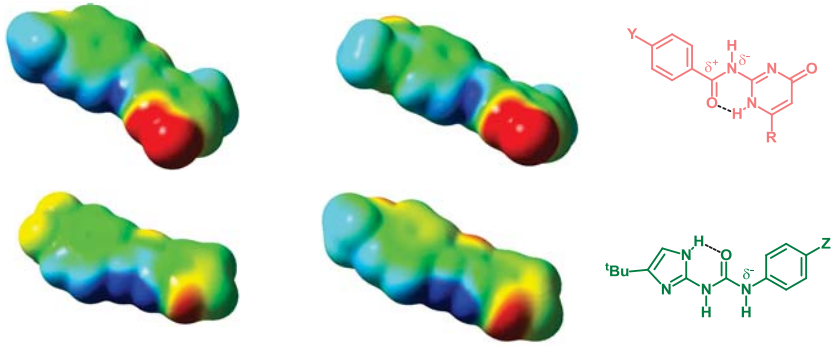

A. Gooch, A. M. McGhee, M. L. Pellizzaro, C. I. Lindsay, A. J. Wilson, *Org. Lett.*, **2011**, *13*, 240-243.

Synthesis of a Urethane Macromonomer

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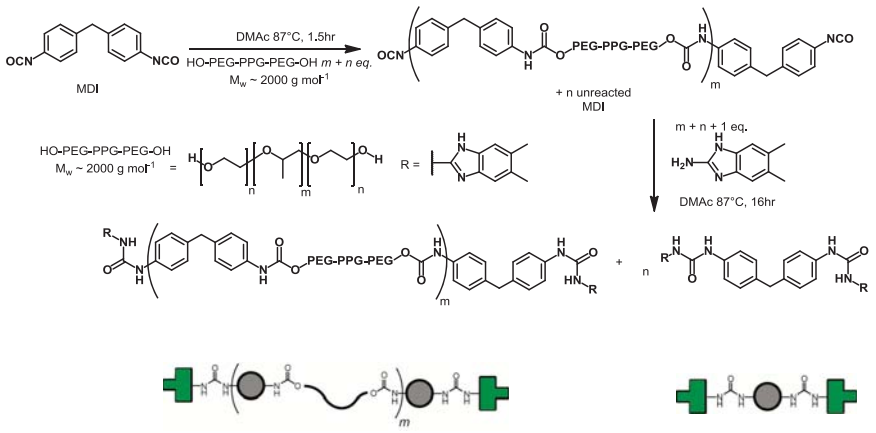

A. Gooch, C. Nedolisa, K. Houton, C. I. Lindsay, A. Saiani, A. J. Wilson, *Macromolecules*, **2012**, *45*, 4723-4729

Hydrogen-Bond-Assembled Material

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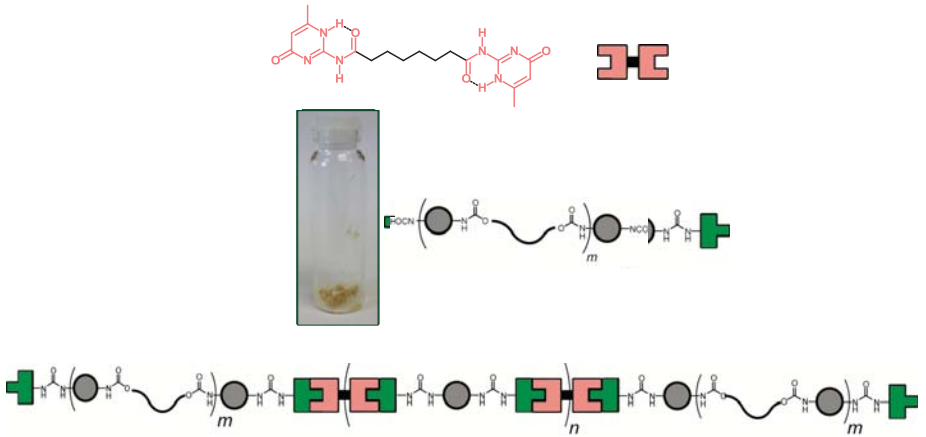

A. Gooch, C. Nedolisa, K. Houton, C. I. Lindsay, A. Saiani, A. J. Wilson, *Macromolecules*, **2012**, *45*, 4723-4729

Self-Sorting of Linear Arrays

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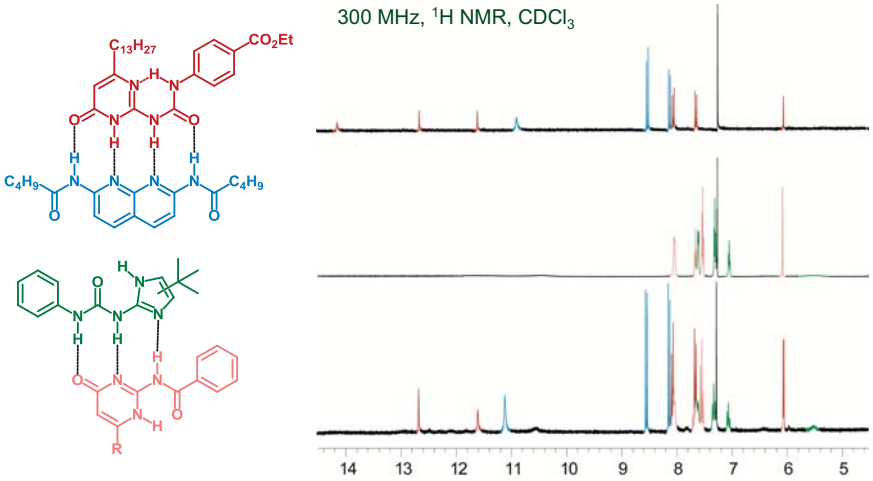
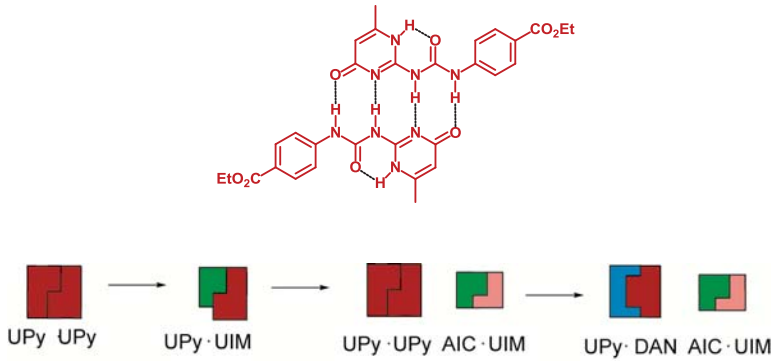


M. L. Pellizzaro, K. A. Houton, A. J. Wilson, *Chem. Sci.*, **2013**, *4*, 1825-1829

Mimicry of Biological Signalling Cascades Employing Self-Sorting Linear Arrays

UNIVERSITY OF LEEDS



M. L. Pellizzaro, K. A. Houton, A. J. Wilson, *Chem. Sci.*, **2013**, *4*, 1825-1829

α-Helix Mediated Protein-Protein Interactions

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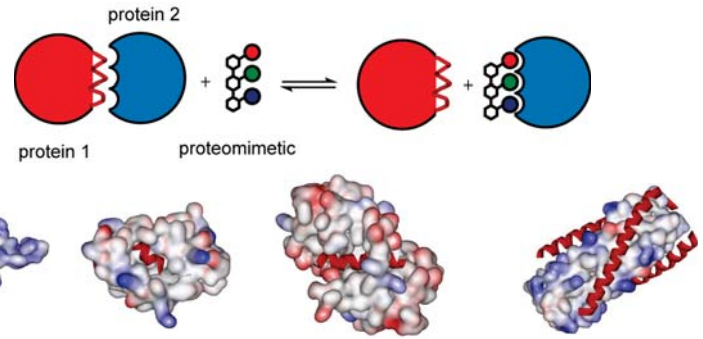

Bcl_2-Bak (1BXL) regulators of apoptosis

p53-hDM2 (1YCR) tumour suppressor

Calmodulin-phosphatase/ kinase (1CDL) controls intracellular Ca^{2+}

gp41 hexameric coiled-coil (1AIK) HIV viral fusion

About 30% of all protein secondary structure comprises α-helices.

T. A. Edwards, A. J. Wilson, *Amino Acids*, **2011**, *41*, 743-754 and V. Azzarito, K. Long, N. S. Murphy, A. J. Wilson, *Nature Chem.*, **2013**, *5*, 161-173.

Designed Inhibitors of PPI – Constrained Peptides

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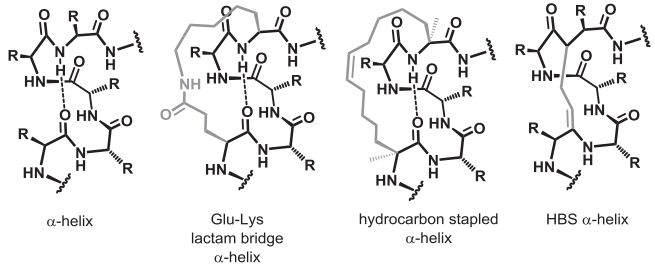

α-helix

Glu-Lys lactam bridge α-helix

hydrocarbon stapled α-helix

HBS α-helix

Constrained peptides

S. K. Sia, P. A. Carr, A. G. Cochran, V. N. Malashkevich and P. S. Kim, *Proc. Natl. Acad. Sci. U. S. A.*, **2002**, *99*, 14664-14669. see also: R. S. Harrison, et al., *Proc. Natl. Acad. Sci. U. S. A.*, **2010**, *107*, 11686-11691, L. K. Henchey, et al., *J. Am. Chem. Soc.*, **2010**, *132*, 941-943. R. E. Moellering, et al. *Nature*, **2009**, *462*, 182-188, M. L. Stewart, et al., *Nat. Chem. Biol.*, **2010**, *6*, 595-601.

Synthesis of Amino Acids

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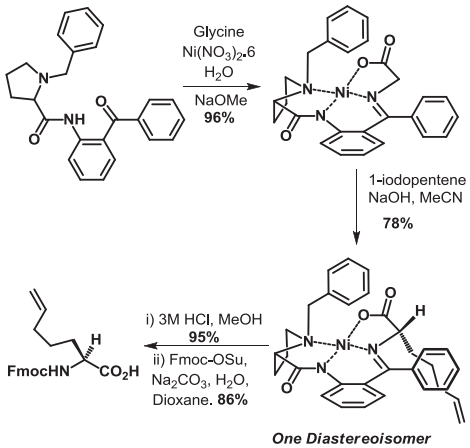

Comparison of Stapled Peptide Potency

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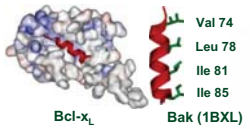
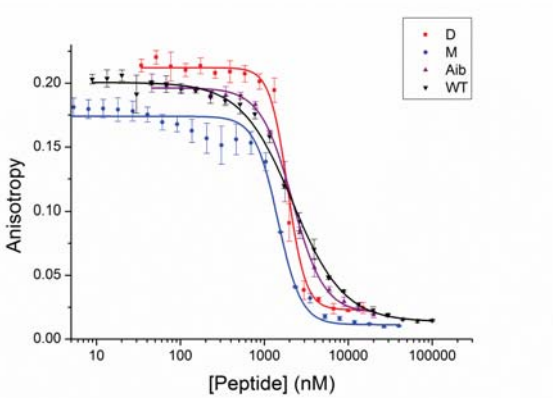


Tested against BAK:Bcl-x_L, a homologous interaction.

Peptide	IC_{50} (μM)
DM	1.89 ± 0.09
MM	1.60 ± 0.04
Aib	2.15 ± 0.05
WT	2.16 ± 0.06

Displacement of BODIPY-BAK (43.6 nM) with Bcl-xL (131 nM) in 40 mM Phosphate, 200 mM NaCl, 0.02 mg/ml BSA pH 7.50.



All IC_{50} values are similar, despite the prediction that an **increased conformational rigidity** of the stapled peptides would, in turn **increase the potency** of inhibition.

D. J. Yeo, S. L. Warriner, A. J. Wilson, *Chem. Commun*., **2013**, 49, 9131-9133

Characteristic Features of α-Helix Mediated PPIs A Model PPI: p53-hDM2

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Often, the *i*, *i* + 3 or *i* + 4 and *i* + 7 or *i* + 8 chains of an α-helix are found to play a critical role in a protein-protein interaction.

p53 is a transcription factor that initiates apoptosis – it is deactivated in many human cancers. HDM2 transcription is induced after p53 activation and negatively regulates p53 by:

Physically blocking activation by direct interaction

Targeting p53 for degradation by ubiquitinylation

Kessler *et. al. Angew. Chem. Int. Ed.* **2006**, *45*, 6440-6460, Kussie *et al. Science*, **1996**, *274*, 948-953, Vassilev *et. al. Science*, **2004**, *303*, 844-848

Oligobenzamide Proteomimetics

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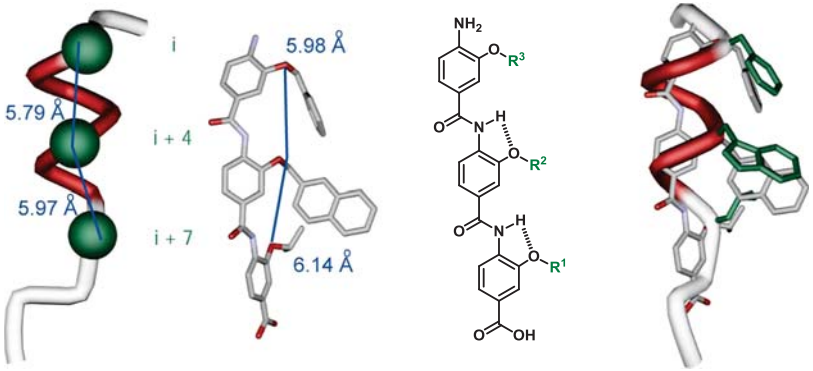

'easy (?) to make' amide bonds connect the monomers – approach amenable to solid phase

For foldamers see: S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 178-190, for bioactive foldamers see: De Grado *et. al. Nat. Chem. Biol.* **2007**, *3*, 252-262, for aromatic oligoamides see: Huc, Gong, Li, Jiang, Zeng, Hamilton

D. L. Boger *et al. J. Am. Chem. Soc.*, **2009**, *131*, 5564-5572, A. D. Hamilton, *et al. Angew. Chem. Int. Ed.,* **2008**, *47*, 9691-9694, J.-M. Ahn and S.-Y. Han, *Tetrahedron Lett.*, **2007**, *48*, 3543-3547

HIF1α/p300 as a Key PPI target In cancer metabolism

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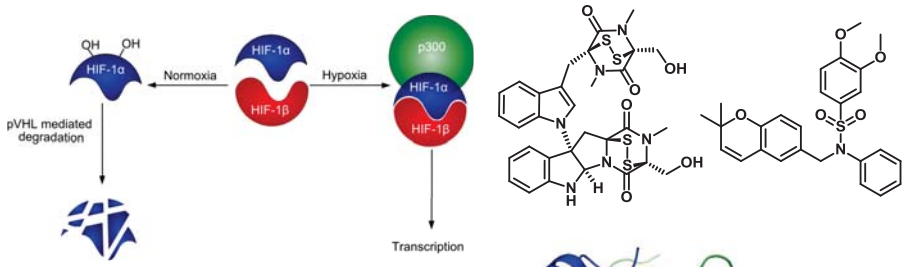

- HIF-1α only present under
- Leads to expression of VE
- Blood supply to tissue rest

PDB ID: 1L8C

JBC, **2009**, *284*, 26831 *J. Med. Chem.*, **2012**, *55*, 6738 *PNAS*, **2002**, *99*, 5271

Literature Compound

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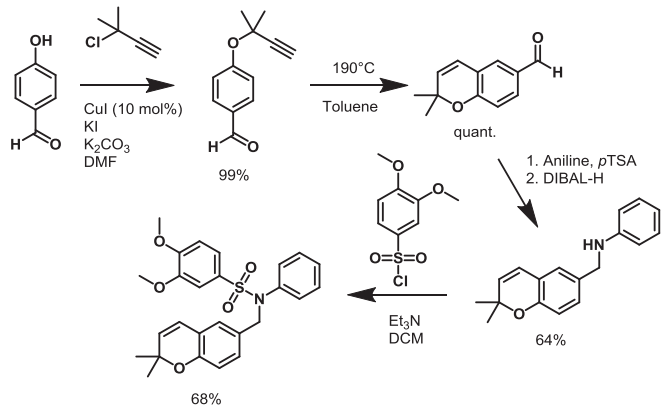

Easy to Make Oligoamide α-Helix Mimetics

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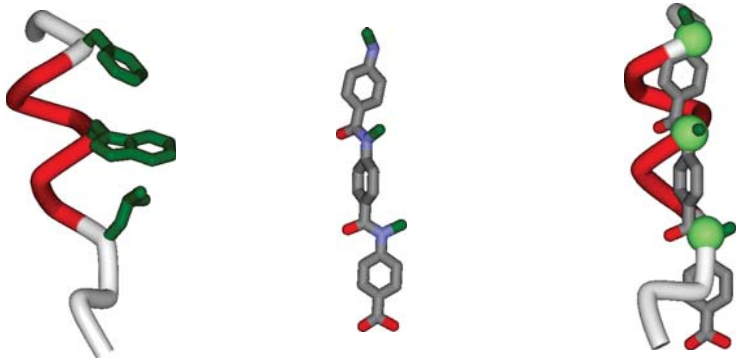

'easy (?) to make' amide bonds connect the monomers – approach amenable to solid phase

For Foldamers see: S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 178-190
For Bioactive Foldamers see: De Grado et. al. *Nat. Chem. Biol.* **2007**, *3*, 252-262

Conformational Analysis

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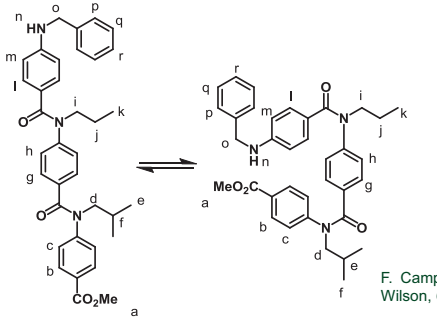
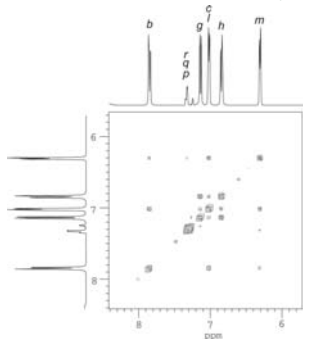


^1H-^1H NOESY (500 MHz, $CDCl_3$)



F. Campbell, J. Plante, C. Carruthers, M. J. Hardie, T. J. Prior, A. J. Wilson, *Chem. Commun.* **2007**, 2240 – 2242.

Cis-Preference Tertiary Benzamides

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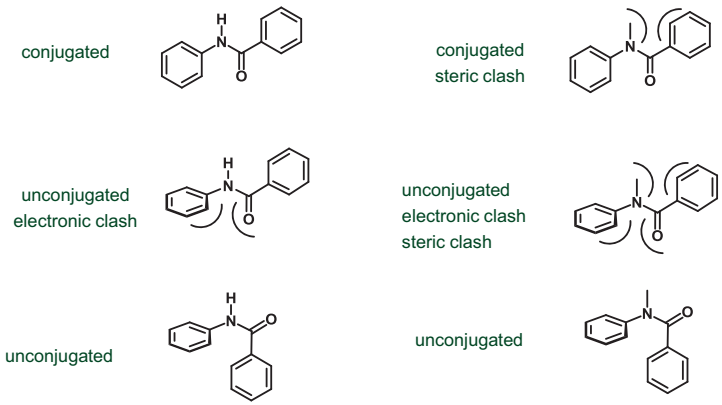

S. Saito, Y. Toriumi, N. Tomioka, A. Itai, *J. Org. Chem.* **1995**, *60*, 4715-4720.

Regiospecifically Functionalised Macrocycles

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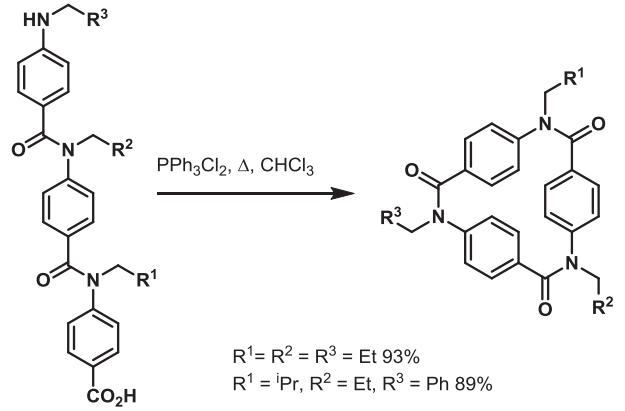

$R^1 = R^2 = R^3$ = Et 93%

R^1 = ^{i}Pr, R^2 = Et, R^3 = Ph 89%

F. Campbell, J. Plante, C. Carruthers, M. J. Hardie, T. J. Prior, A. J. Wilson, *Chem. Commun*. **2007**, 2240 - 2242.
See also: F. Campbell, C. A. Kilner, A. J. Wilson, *Tetrahedron Lett*., **2010**, *51*, 1361-1363.

IC_{50} Determination Selected Compounds

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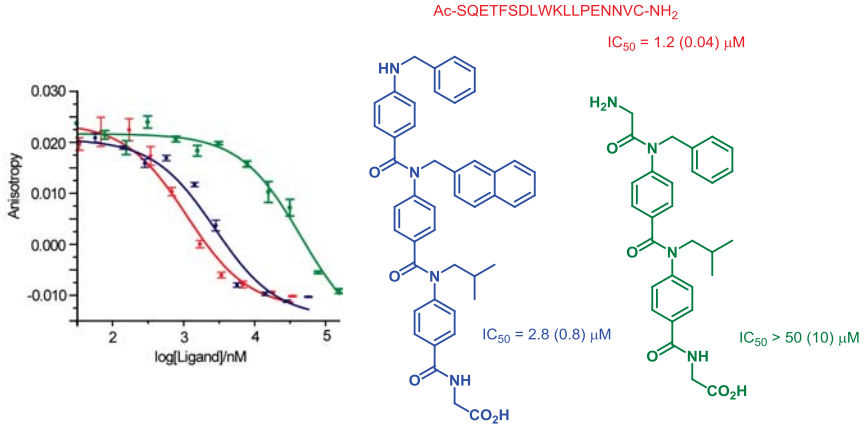

F. Campbell, J. P. Plante, T. A. Edwards, S. L. Warriner, A. J. Wilson, *Org. Biomol. Chem.*, **2010**, *8*, 2344-2351.

Expanded Monomer Set

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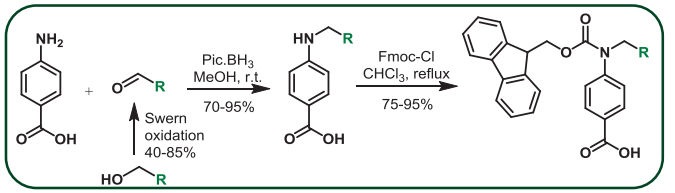

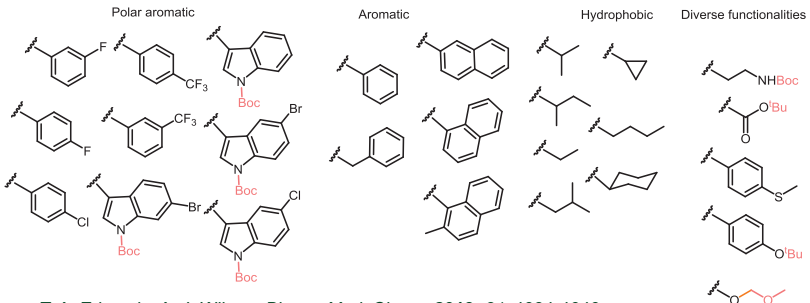

K. Long, T. A. Edwards, A. J. Wilson, *Bioorg. Med. Chem.*, **2013**, *21*, 4034-4040.

Microwave Assisted Solid Phase Synthesis

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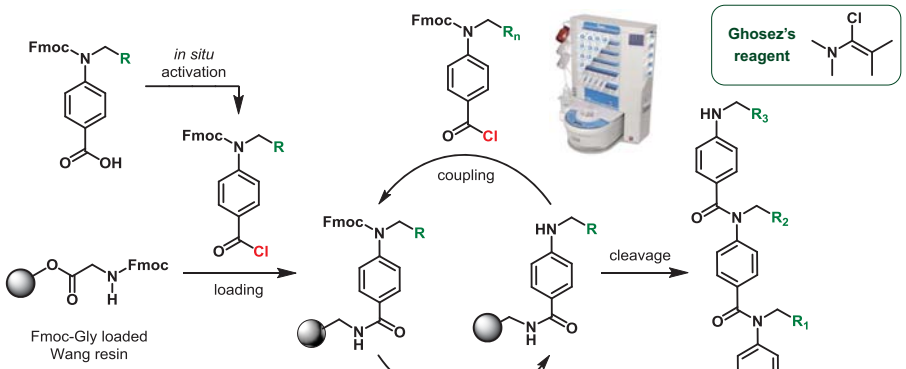

Optimised coupling conditions :

monomer : 2.5 eq. to the resin (per coupling)
Ghosez's reagent : 0.95 eq. to the monomer
preactivation : 1h, r.t., $CHCl_3$
coupling : 2×20min, 60 °C

K. Long, T. A. Edwards, A. J. Wilson, *Bioorg. Med. Chem.*, **2013**, *21*, 4034-4040.

Synthesis of Labelled Analogues

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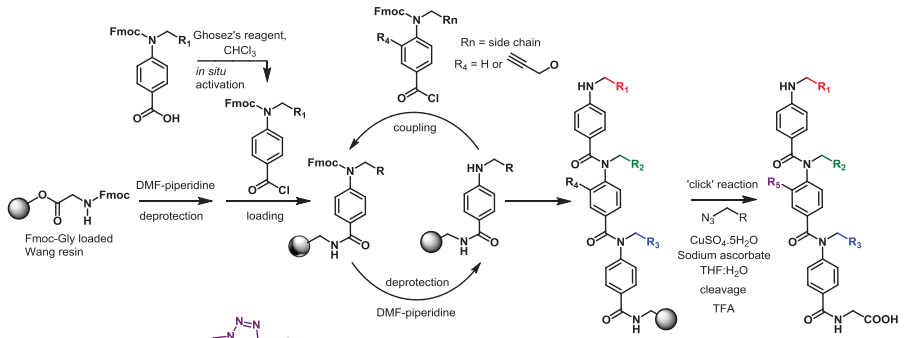

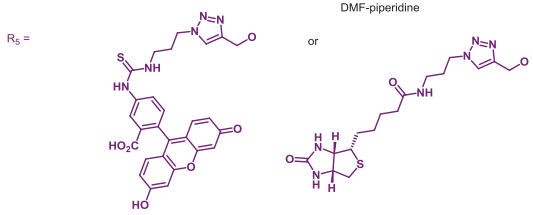

For development of synthetic method see: A. Barnard, K. Long, D. J. Yeo, J. A. Miles, V. Azzarito, G. M. Burslem, P. Prabhakaran, T. A. Edwards, A. J. Wilson, *Org. Biomol. Chem.*, **2014**, *12*, 6794-6799