beta/gamma-Peptide manifolds designed as alpha-helix mimetics

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This thesis was devoted to the synthesis and the structural characterisation of beta/gamma-peptides, constructed from beta- and gamma-amino acids in alternation, designed to mimic the alpha-helix secondary structure which is present in many native proteins.

The alpha-helix can be defined as a 13-helix and a bottom-up foldamer design strategy to target a 13-helical structure was examined, whereby beta/gamma-peptides were proposed in which (1S,2S)-trans-2-aminocyclobutanecarboxylic acid (trans-ACBC) was incorporated as a conformationally-restricted beta-amino acid component. The scalable synthesis of enantiomerically pure trans-ACBC using a [2+2] photocycloaddition strategy was successfully optimized. beta/gamma-Peptides incorporating trans-ACBC and GABA, the latter being the gamma-amino acid component devoid of any constraint, were then synthesised. Experimental and theoretical investigations of their solution-state folding behaviour revealed an unprecedented 9/8-ribbon foldamer structure that adopts curved shapes governed by a combined configuration-conformation code.

Additional constraints on the gamma-amino acid component were then considered and beta/gamma-peptides incorporating trans-ACBC and gamma4-amino acids were synthesised. Experimental and theoretical investigations of these beta/gamma-peptides in solution unveiled a preference for 13-helix folding behaviour, which increased commensurately with the peptide chain length; robust 13-helices were stabilised by a minimum of five intramolecular hydrogen bonds.

In the last part of this thesis, molecular modelling was used to design helical alpha/beta/gamma-peptides intended to reproduce as closely as possible the hot-spot residues of the known alpha-helical peptide sequence p53(15-31). These peptides were synthesised and their predicted helical folding was verified experimentally along with their resistance to proteolytic enzymes. The alpha/beta/gamma-peptides were tested as inhibitors of the p53/hDM2 interaction. One peptide was found to behave as potent inhibitor and to bind to the native peptide binding pocket of the hDM2 protein, providing a successful proof of concept of the alpha-helix mimetic design strategy.