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Alpha-Helix Mimetics

Mimetica's technology can also be applied to form alpha-helix mimetics, potentially leading to stabilised forms of helical peptide hormones. Mimetics having a covalent hydrogen bond replacement (Figure 1, C) can be made with Mimetica's technology – an approach that has not been achieved previously. Reducing this technology to practice forms the basis of an ARC Linkage grant between the University of Queensland and Mimetica.

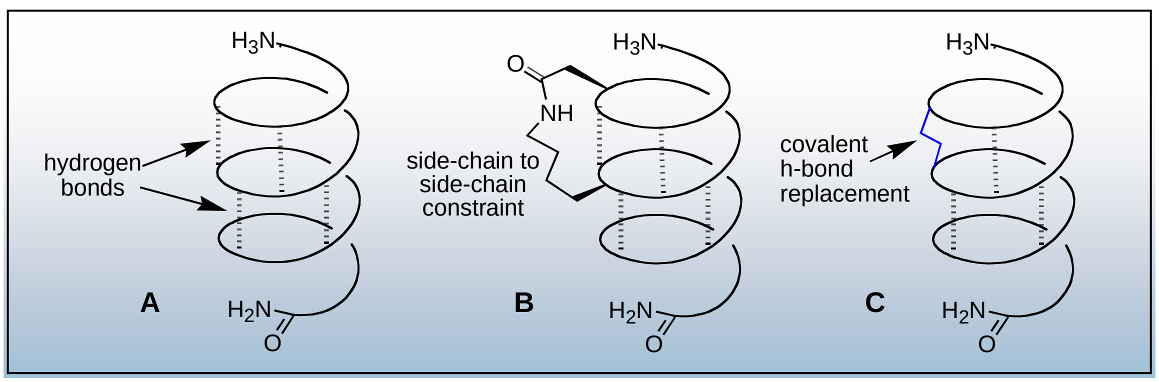

Figure 1. *Stabilisation of Alpha-Helices.*
A*: The natural helix is stabilised by weak backbone hydrogen bonds.*
B*: Side-chain to side-chain constraints have been demonstrated in some systems, but the approach is indirect and can interfere with receptor binding.*
C*: Covalent replacement of the backbone hydrogen bond. Approach C minimizes disruptions to side chain substituents, and is possible for the first time with Mimetica's technology.*

Initial results have shown that one of the isomers of the macrocyclic helical turn mimetic with a covalent hydrogen-bond replacement has a circular dichroism (CD) spectrum characteristic of an alpha helix (Figure 2). This is an exciting and significant scientific result as the mimetic is only 5 residues long. This may be of significant commercial importance if the helical turn mimetic can be used to stabilize truncated versions of therapeutically important peptide hormones such as parathyroid hormone (osteoporosis) or GLP-I (type II diabetes), improving their drug-like properties.

mimetica
PEPTIDE MIMETICS

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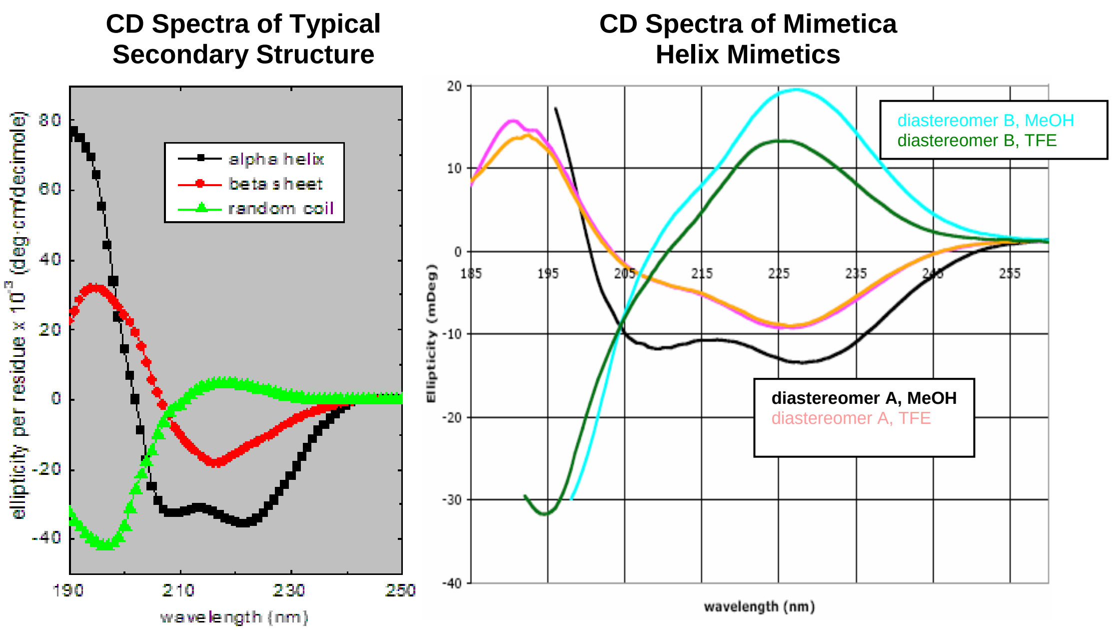

Figure 2. *Proof of concept for Mimetica's helical mimetics – a pentapeptide mimetic gives a distinctly helical spectrum. This is the first reported full internal helical mimetic.*

The helical turn mimetic may also be applied to helices involved in protein-protein interactions, such as those as illustrated below. Figure 3 shows the helical structure (in green) of a peptide bound to a protein involved in controlling apoptosis – programmed cell death. Blocking this interaction is thought to be an attractive approach to treating a range of cancers. Mimetica's helix mimetic technology may allow the creation of shorter stabilized versions of the peptide helix that are more likely to have drug like features of stability and permeability than the peptide shown. Producing small molecule drugs to block this type of protein-protein interaction has been very difficult for traditional pharmaceutical chemistry. Our technology could enable an effective approach to this class of targets. Another example of such a helical interaction site is shown in Figure 4 – this is also a cancer target.

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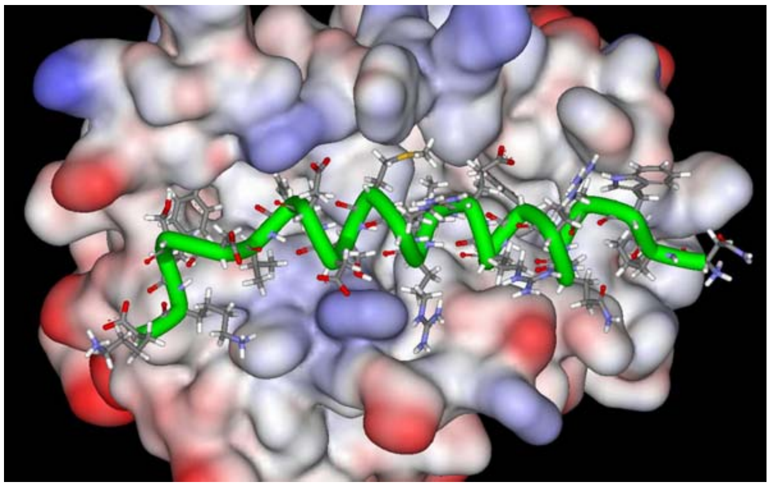

***Figure 3**: Bad peptide (helical, green) bound to the protein Bcl-x_L (PDB Structure 1G5J).*

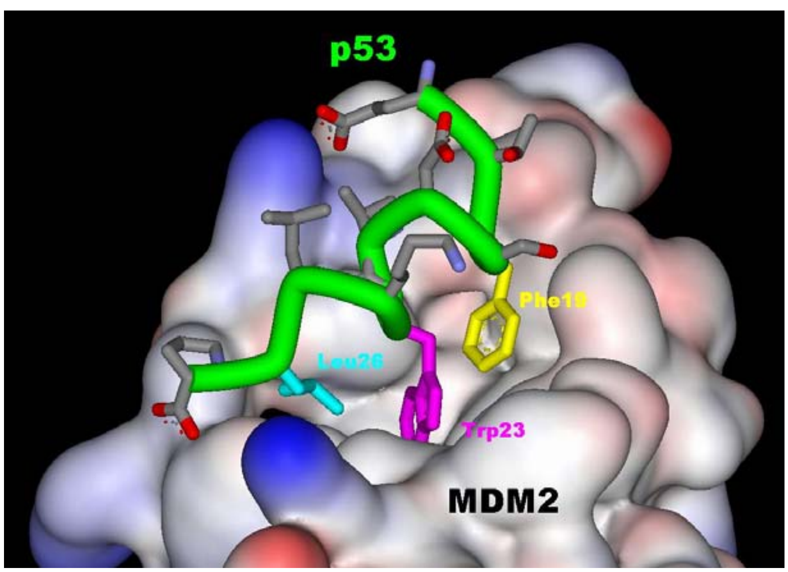

***Figure 4**: Helical domain of the p53 tumour suppressor protein (green) bound to the MDM2 protein with the key F19,W23,L26 residues highlighted (PDB structure 1YCQ)*

To produce more drug-like mimetics of these native helical peptides the covalent H-bond mimetic would be substituted into the centre of the helix and both ends would be truncated and modified to optimise binding. For a Type II GPCR hormone truncation could only take place at one end as the N-terminus is typically required to maintain agonist potency. Truncated helix mimetics could potentially have a molecular weight of < 1000 and are likely to possess improved bioavailability.