Oxetane Based Peptidomimetics: Potential New Tools for Drug Discovery and Chemical Biology

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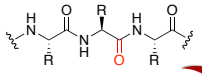
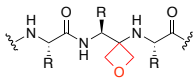
Oxetane Modified Peptides: Why?

Peptide based drugs[1] present significant challenges with respect to bioavailability and biostability, partly because they are labile *in vivo* to the action of peptidases and proteases. Chemical modification of the peptide bond is an established strategy to improve the effectiveness of a drug candidate by increasing its bioavailability, serum half-live and selectivity for the target receptor.[2] **Here, we report a new type of peptide bond isostere, in which the heterocyclic oxetane nucleus is used as a replacement for the carbonyl group within the peptide backbone.[3]**

Conventional peptide:



Oxetane modified peptide (OMP):

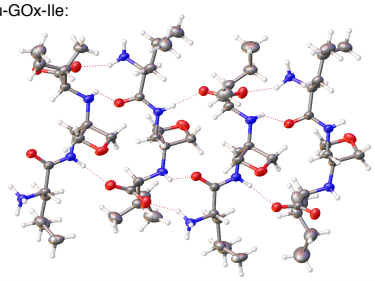


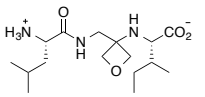
This approach has a number of attractive features:

- Oxetanes are excellent bioisosteric replacements in conventional, small-molecule drug discovery where they often enhance **metabolic stability and lipophilicity**;[4]
- Oxetane modified peptides (OMPs) should have **greatly reduced vulnerability to proteases**;
- Any α-amino acid in a peptide chain could be replaced providing enormous opportunity to control **structure and function**;
- OMP residues should participate in **H-bonding interactions**, as both donor and acceptor;
- Conformational changes will provide access to new **peptide "structural space"**;
- OMPs should be relatively **easy to make**.

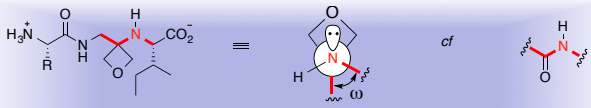
Oxetane Peptidomimetics: Structural Insights by XRD

Leu-GOx-Ile:





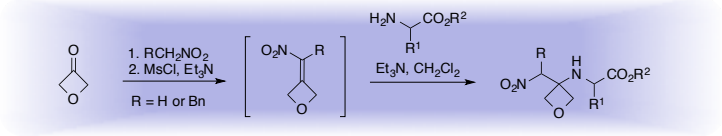
- Observe anti-parallel sheet-like arrangement in the solid state.
- Aminooxetane unit acts as H-bond donor and acceptor.
- 'Normal' zwitterionic structure seen *i.e.* secondary amine not protonated



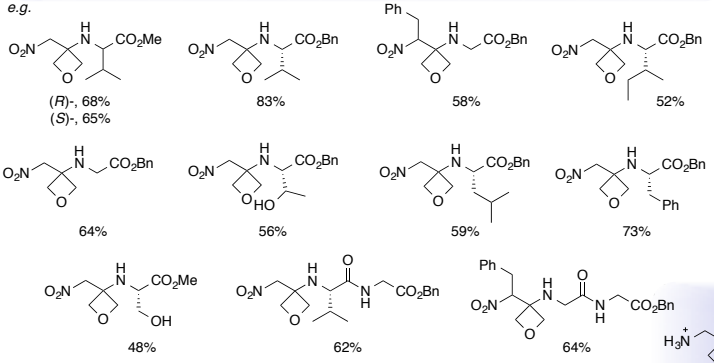
Nitrogen hybridization and dihedral angle changes occur upon amino-oxetane substitution allowing access to new peptide "structural space".

Simple Preparation Of Oxetane Containing Peptidomimetics

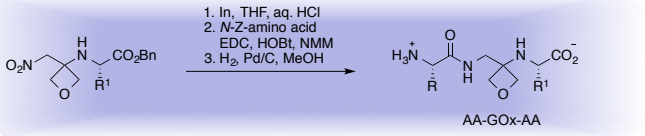
Step 1: Introduction of Oxetane by Conjugate Addition



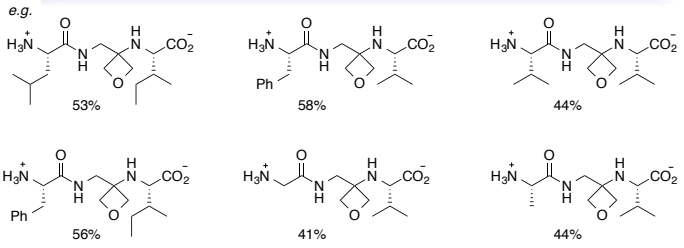
e.g.



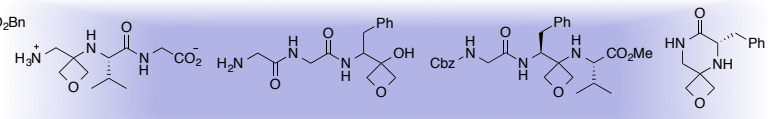
Step 2: Nitro Group Reduction/Homologation



e.g.



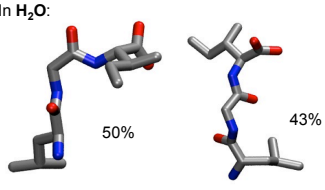
***Additional types of modifications** (chemistry not shown):*



A practical route to aminooxetane containing tripeptides has been established with full scope currently being explored.

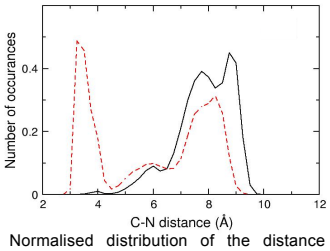
Oxetane Peptidomimetics: Molecular Dynamics Simulations

In **H_2O**:



Snapshots of the two most populated clusters of **Leu-Gly-Ile** (top) and **Leu-GOx-Ile** (bottom), with percentages of total structures accounted for by each cluster.

- Conformations explored by **Leu-Gly-Ile** are dominated by extended structures with C and N termini separated by >7 Å.
- Most populated cluster of **Leu-GOx-Ile** is folded with C and N termini separated by 3–4 Å. Close contact between the terminal $-CO_2^-$ and $-NH_3^+$ ions.



Normalised distribution of the distance between the C- and N-termini: **Leu-Gly-Ile** (black) and **Leu-GOx-Ile** (red dotted).

In MD simulations, turn-like features are favoured.

Future Work

- Demonstrate that these peptidomimetics are useful in medicinal chemistry programmes;
- Further generalise the chemistry, and translate the methodology to the solid-phase;
- Investigate how various secondary structural motifs of peptides are influenced by the introduction of one or more oxetane modified residues.

Acknowledgements

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References

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2. For reviews, see I. Avan *et al*, *Chem. Soc. Rev.* **2014**, *43*, 3575; R. M. J. Liskamp *et al*, *ChemBioChem* **2011**, 12, 1626; A. Grauer and B. König, *Eur. J. Org. Chem.* **2009**, 5099; J. Vagner *et al*, *Curr. Opin. Chem. Biol.* **2008**, *12*, 292.
3. N. H. Powell *et al*, *Chem. Commun.* **2014**, 8797. For related work by Carreira, see M. McLaughlin *et al*, *Org. Lett.* **2014**, *16*, 4070.
4. G. Wuitschik *et al*, *J. Med. Chem.* **2010**, *53*, 3227.