**Synthetic Conformationally Constrained Peptides**

Most naturally occurring constrained peptides maintain the rigidity of the peptide framework by disulfide bond or N- to C-termini backbone cyclization. Commonly known antimicrobial peptides like Gramidicin S, Bacitracin and Polymyxin B are an example of backbone cyclic peptides that are used clinically (Table 1).[1]

Table 1: Natural cyclic peptides

| **Peptide** | **Structure** |
|---|---|
| Gramicidin S | Cyclic (LOVPF$^{d}$LOVPF$^{d}$) |
| Bacitracin | Cyclic I(C )LE$^{d}$I(KO$^{d}$IFHD)D$^{d}$-$NH_2$ |
| Polymyxin B | Cyclized Octanoyl BTBB(BF$^{d}$LBBT) |

Parenthesis indicate amino acids that are cyclized, $^{d}$ the D-enantiomer; O, Ornithine; B, diaminobutyrate

Conotoxins are another class of small peptide ligands (typically 10-30 amino acids) highly crosslinked by disulfide bonds.[2] Despite their small size, these peptide ligands have very high affinities and selectivities to their cognate receptors and many of them have now become standard research tools in neuroscience.

Although cysteine bridges are quite common structural motifs in naturally occurring peptides like neurotoxins,[2] cyclotides,[3] somatostatin[4] and insulin superfamily[5], disulfide bridges (Figure 1) are readily reduced to their acyclic thiol form in an intracellular environment. Thus scientists have derived new methods of inducing stable conformation constraint of many peptides. For instance, advancement of organometallic chemistry has led to use of phase transfer catalyst like Grubbs catalyst[6] in ring closing metathesis. This chemistry has been utilized by Gregory Verdine to synthesize stapled peptides which have been found with promising biological functions (Figure 2A, Table 2) [7].

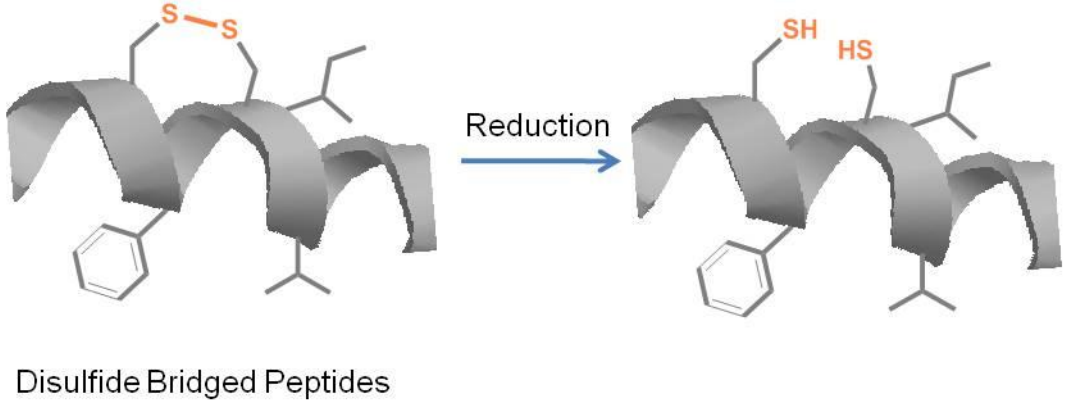


Figure 1: Scheme showing reduction of disulfide bonds in cellular environment to acyclic thiol.

In addition, availability of variety of protecting groups for amines and carboxylic acids which are cleavable under orthogonal conditions have made amide bond lactam bridges to be an alternative covalent linkage substituting disulfide bonds (Figure 2B).

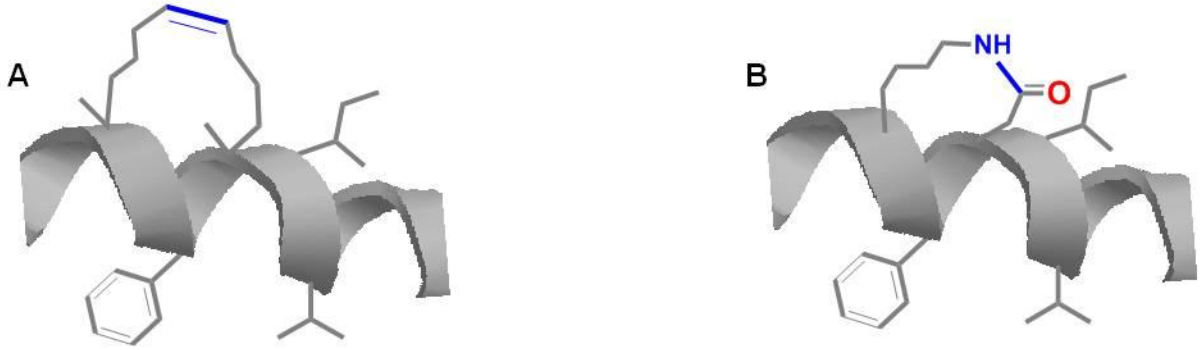


Figure 2: (A) Hydrocarbon stapled peptides synthesized through ring closing metathesis, (B) amide bond lactam bridge

As summarized in the table 2 below, several synthetic cyclic peptides have shown desirable biological properties over their linear counterparts.

Table 2: Examples of constrained peptides with attractive biological properties

| **Peptide** | **Type of Modification** | **Properties** | **References** |
|---|---|---|---|
| α-Conotoxin | N- to C- terminus cyclization | Increased stablility in human plasma | Clark *et al*. *Proc Natl Acad Sci USA* **2005**, *102*, 13767ï 13772. |
| BID BH3 | Hydrocarbon stapling using ring closing metathesis | Increased protease resistance and serum stability | Walensky *et. al.,* Science, **2004**, *3*, 1466-1470 |
| NOTCH1 | Hydrocarbon stapling using ring closing metathesis | Increase binding affinity towards NOTCH transactivation complex | Raymond E. M., Melanie C., Tina N. D., Cristina Del Bianco, Jon C. A., Stephen C. B., Andrew L. K., D. Gary G., Gregory L. V., James E. B., *Nature **2009**, **462,*** 182-188. |
| Glucagon-like Peptide-1 | Side chain to side chain *i, i+4* lactam bridge formation | Increased receptor efficacy and enzyme stability | Murage E. N. Gao G., Bisello A., Ahn J-M. *J. Med. Chem.* **2010**, *53*, 6412-6420 |
| DP178 (HIV35) | Side chain to side chain *i, i+7* lactam bridge formation | Increase HIV inhibitory activity as a result of stabilized α-helical conformation | Judice *et. al.,* Proc. Natl. Acad. Sci. USA. **1997**, *94*, 13426-13430 |

## References


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