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Ring-closing Metathesis in Peptides

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ABSTRACT

This review highlights developments in the field of ring-closing metathesis applied to the synthesis of cyclic peptides. Special attention is focussed on the synthesis of dicarba peptides that mimic native cystine containing peptides. Recent advances in the field are discussed, including the stereoselective synthesis of carbon-bridged peptides and RCM in aqueous media.

Introduction

Peptides and proteins are essential for an array of vital processes within living organisms, such as hormones, transmembrane carriers and enzymes.[1,2] Their molecular complexity results in exquisite selectively towards biological targets, leading to compounds that are highly potent with limited off-target side effects.[3] As such, there is increasing interest in the use of peptides as pharmaceuticals.[4] Biological applications of peptides include vaccines,[5-7] medical imagining technologies[8,9] and drug delivery systems.[10,11] However, the poor resistance of many peptides to proteolytic enzymes, poor bioavailability, and rapid clearance limits the full potential of these molecules as therapeutics.[12] Thus, the design and development of novel peptidomimetics that have increased metabolic stability, functional selectivity and increased oral availability while maintaining potent native activity continues to attract considerable attention from the peptide community.[13]

The creation of peptides containing non-natural linkages within the active sequence is one way of increasing bioavailability of native peptides without altering their biological activity.[13] Cyclic peptides found in nature form constrained three-dimensional structures that often have diminished sensitivity towards degradation by enzymes.[14] Furthermore, the constrained structural framework of cyclic peptides results in less conformational freedom compared with their linear counterparts, reducing unfavorable entropic effects and thus increasing their receptor binding affinity.[1] Chemists can insert metabolically inert bridges into sequences to enhance stability and bioactivity. Formation of the cyclic topography can be achieved *via* head-to-tail cyclisation of the *N*- and *C*-termini of the peptide[3,15] or by ligation of sidechains of coded and uncoded amino acids. The latter approach furnishes bridging units such as lactams,[16,17] 1,2,3-triazoles,[18,19] thioethers,[20-23] diselenides[24-27] and dicarba bridges,[28-30] the last of which will be discussed further in this review (Figure 1).

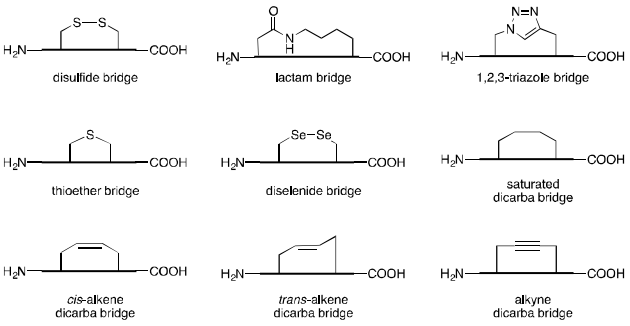

Figure 1. Cyclizing motifs used in peptidomimetic chemistry

Olefin metathesis has emerged as a powerful synthetic tool for the construction of C-C bonds.[31,32] Notably, the high catalytic activity and exceptional functional group tolerance of commercially available Ru-alkylidene olefin metathesis catalysts has led to the popularity of this reaction (Figure 2).[33-36] Significantly, the robustness of these catalysts has enabled application of olefin metathesis to large, highly functionalized biomolecules such as peptides. The resultant carbon-based linkage has been used as a dicarba surrogate of naturally occurring disulfide bridges, and has been shown to enhance α-helical and β-turn motifs and hence secondary tertiary structure in peptide sequences (e.g. 'stapled' peptides).[28-30] As stapled

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