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Digest paper

Recent developments in peptide macrocyclization

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ABSTRACT

Cyclic peptides have been widely applied in fields ranging from drug discovery to nanomaterials. After years of development, the preparation of peptide macrocycles, especially late-stage macrocyclization of peptides, remains challenging using traditional synthetic methods. This digest highlights recent developments in the synthesis of cyclic peptides.

Contents

Introduction

Naturally occurring peptides and peptidomimics are rich in structural diversity and biological activities. As an important source of drug candidates, peptide compounds have attracted increasing attention in both chemical and pharmaceutical communities. As the landmark of peptide natural products used in clinic, gramicidin S was widely employed as a broad-spectrum antibiotic in the treatment of septic gunshot wounds during the Second World War (Fig. 1).[1] Nisin, which belongs to the family of ribosomally synthesized and posttranslational modified peptides (RiPPs), has been used as antibiotic preservative in food industry for over 90 years without significant development of drug-resistance (Fig. 1).[2–4] Another example, celogentin C (Fig. 1), a non-ribosomal cyclic peptide natural product containing a unique overlapping ring topology through Trp C6-Leu Cβ and Trp C2-His N1 crosslinks, exhibited strong inhibitory activity towards tubulin polymerization.[5–7] Up to date, thousands of peptide compounds have been discovered from natural sources or synthesized with diverse bioactivities including antimicrobial, antivirus, antitumor and immunosuppressive activities and a number of them have been employed as clinical drugs and in food industry.[8]

Synthetic cyclic peptides have experienced exponential growth in recent years, mostly due to their potential as drug candidates and biological tools, especially towards targets such as protein-protein interactions (PPIs), which are usually difficult to regulate with small molecule compounds (less than 500 Da).[8] In this digest,

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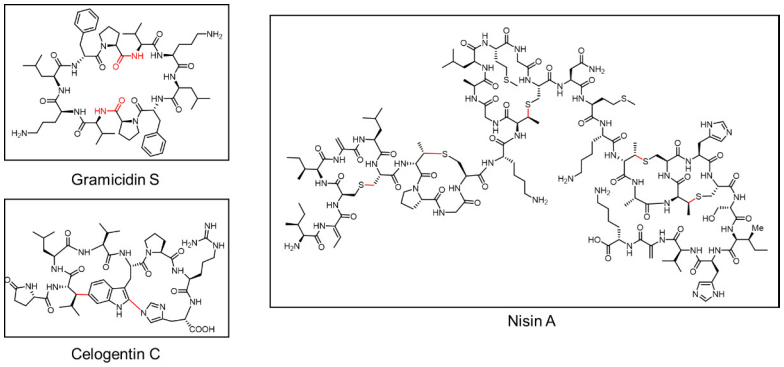

Fig. 1. Examples of cyclic peptide natural products.

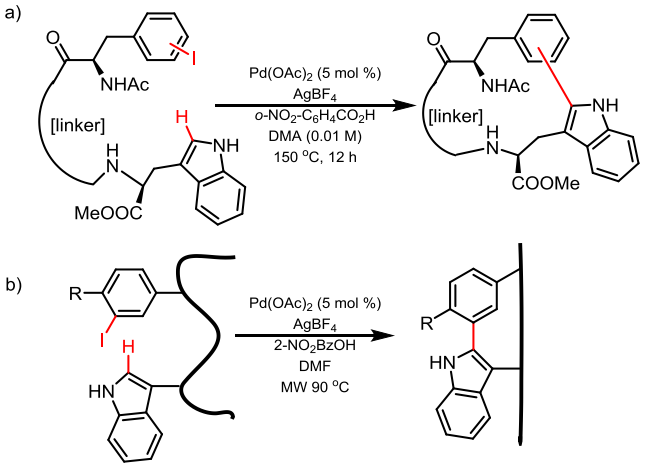

Fig. 2. Palladium-catalyzed peptide macrocyclization.

we include methods that have been developed in recent years towards the syntheses of cyclic peptides with structural diversity. Classic peptide macrocyclization strategies including amide bond and disulfide bond formation, RCM and azide-alkyne cyclization have been extensively reviewed elsewhere, and therefore are not the focus of this review.[9–14] Herein, recent advances in cyclic peptide synthetic strategies emerged in the past 5 years will be discussed.

Transition metal catalyzed peptide macrocyclization

Peptide macrocyclization often relies on functional natural amino acids (Lys and Cys residues) or the incorporation of unnatural amino acids (for azide-alkyne and RCM cyclization), limiting the structural diversity of resulting cyclic peptides. Recently, transition metal catalyzed C-C formation has emerged as an efficient method for peptide modification and macrocyclization through the activation of "inert" C-H bonds of amino acid side chains.

Pd-catalyzed peptide macrocyclization was first reported by James and co-workers following an intramolecular coupling between a tryptophan residue and a halophenyl-containing amino acid (Fig. 2a).[15] The C-H activation process was highly selective toward the C-2 position of the tryptophan indole by constructing a Trp C2-Phe C-C crosslink. The reaction proceeds at mild conditions that tolerate a range of functional groups and allow direct access to 15- to 25-membered indole-aryl bridged macrocycles in good yield, which allow its potential utility in pharmaceutical discovery setting.

Lavilla and Albericio group further optimized this reaction with the assistance of microwave irradiation, which significantly shortened the reaction time. This reaction was therefore applied to construct cyclic peptides featuring a covalent bond between tryptophan and phenylalanine or tyrosine residues (Fig. 2b).[16,17] This method allowed the preparation of cyclic peptides of complex topologies, and a number of cyclic peptides exhibited improved stability, cell permeability and biological activities.[17]

Recently, Albericio group[18] and our group[19] have independently developed a robust procedure to generate cyclic peptides containing unique Cβ-Ar crosslinks through Pd mediated intramolecular

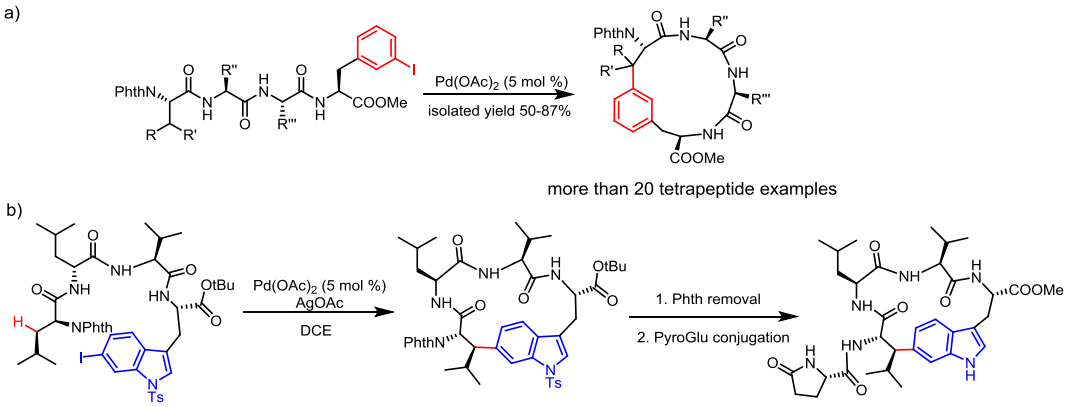

Fig. 3. Site-selective macrocyclization via intramolecular reaction.