A combinatorial approach towards pharmaceutically relevant cyclic peptides

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Chapter 6

Retrospection and Outlook

Abstract: This thesis deals with new developments for a combinatorial synthesis of cyclic peptides. Different newly developed approaches have been described in Chapters 2-5. In this final chapter, the previous chapters will be evaluated and possible future topics for further investigation are indicated.
6.1 Auxiliary-mediated synthesis of medium-sized bis(lactams)

The optimized auxiliary allowed the sequence independent synthesis of seven-membered bis(lactams) (Chapter 2). Although the auxiliary-mediated synthesis of eight-membered rings succeeded with the remainings of the auxiliaries still attached, final auxiliary removal was extremely difficult, due to the ring strain in the eight-membered rings of both the auxiliary-attached bis(lactams) and the final bis(lactams). To investigate this further, different substituted eight-membered bis(lactams) might be new targets (Figure 6.1), not only derived from an α and γ amino acid (1-2), but also derived from two β amino acids (3). The N-alkylated amide bond present in these peptides as well as a different position of the amide bonds in 3 might prevent the unwanted transannular reactions of the products after and during the auxiliary removal. Besides bis(lactams), the auxiliary can also be used to synthesize different cyclic tetrapeptides.

**Figure 6.1** Possible eight-membered bis(lactams) as targets.

![Figure 6.1 Possible eight-membered bis(lactams) as targets.](image)

Although the auxiliary was successfully modified to allow immobilization on a resin, on resin auxiliary-mediated cyclizations were still unsuccessful. Various conditions for the N-Alloc/OAll removal may be applied in combination with resins with different swelling properties.

6.2 Backbone amide linker strategy for the synthesis of 1,4-triazole-containing cyclic peptides

An efficient backbone amide linker was developed for the synthesis of 1,4-triazole-containing cyclic tetra- and pentapeptides (Chapter 3). However, the linker suffered from steric hindrance at the first amino acid next to the linker. For this reason, propargylamine had to be used in the condensation with the aldehyde linker.

**Scheme 6.1** Modified linker for O→N acyl transfer mechanism coupling of amino acids.
Modification of the linker should also make it suitable for sterically hindered sequences, by means of an O→N or S→N acyl transfer reaction similar to the auxiliary of Chapter 2 or the methods developed for traceless native chemical ligation (Scheme 6.1).\textsuperscript{1,2}

Starting from a linker with a free OH or SH instead of the original methoxy group, the first substituted amino alkyne will be condensed to the linker 4. Coupling of the next amino acid can now proceed at the less hindered hydroxyl or thiol group of the linker 5, after which the amino acid is ‘delivered’ to the amine by an intramolecular O→N acyl shift to arrive at 7. This would open up the possibility of new targets.

### 6.3 Synthesis of 1,5-connected triazole-containing cyclic peptides

An approach for the synthesis of 1,5-connected triazole-containing cyclic pseudotetrapeptides has been described (Chapter 4). Although several derivatives of the natural cyclic peptide cyclo-[Pro–Val–Pro–Tyr] have been made, this method is not suited for a combinatorial approach to 1,5-connected triazole-containing cyclic pseudopeptides. The use of the linker developed for the combinatorial synthesis of 1,4-connected triazole-containing cyclic peptides described in Chapter 3, may also be used for these cyclic pseudopeptides (Scheme 6.2). However, the design should be slightly altered because the ruthenium-catalyzed cycloaddition reaction is not suited for a macrocyclization reaction. Starting from the alkyne-containing linker (9), several N-azide substituted dipeptides may be coupled via the ruthenium-catalyzed cycloaddition reaction (10). Elongation at the N-linker via standard N-Fmoc based peptide chemistry should provide a linear precursor (11) suited for macrolactamization.

**Scheme 6.2** Backbone amide linker approach for the synthesis of 1,5-connected triazole-containing cyclic peptides.
Alternatively, 1,5-connected triazole-containing dipeptides may be used in standard solid phase approaches for the synthesis of cyclic peptides. Using a safety catch linker, these units may be incorporated in the growing peptide chain and after activation this would produce the cyclic peptides in a cyclo-release mechanism.

6.4 Combined Ugi-4CR and azide-alkyne cycloaddition reaction for the synthesis of cyclic pseudopeptides

A combined approach has been developed for the synthesis of cyclic pseudopeptides, using the combinatorial character of the Ugi-4CR together with the cyclization power of the copper-catalyzed azide-alkyne cycloaddition reaction. A large variation was shown for the use of different aldehydes and azido acids and azido acid dipeptides, but the variation in isonitriles is still limited. Especially in the case of the cyclic pseudotetrapeptides, different alkyne-containing isonitriles 13-16 might be used containing two similar α-substituents (Figure 6.2). Possibly, even asymmetric α,α-disubstituted isocyan alkynes (17) may be incorporated, although the synthesis of these compounds would be far more challenging. In this way, a three dimensional library may be constructed with different inputs as aldehydes, isonitriles and azido acid dipeptides.

Figure 6.2 Different alkyne-containing isonitriles.

The method already showed its application in the synthesis of natural product analogues. A library of chlamydocin-analogues may now be constructed and evaluation of the biological activity might reveal information about the pharmacophore of the HDACs.

Scheme 6.3 Introduction of side chains in cyclic peptide HDAC inhibitors.

In this context other analogues of natural HDAC inhibitors may also be constructed and used as input in biological screening. In addition, the use of the alkene-containing side chain (18) derived from the aldehyde component should allow the introduction of different types of side chains (19) via a cross metathesis reaction with different alkenes (20) (Scheme 6.3).
6.5 References and notes


