variants to improve key properties such as binding affinity, specificity, stability, pharmacokinetic properties and others, and thus the preparation of large numbers of peptides.

A further major bottleneck in the development of cyclic peptide therapeutics is the chromatographic purification of peptides after synthesis that is expensive due to the sequential processing of each peptide and high reagent consumption (solvents), even when automated and optimized. The main reason for the need of purifications is the macrocyclization reaction, being typically the most difficult step in cyclic peptides synthesis (C.J. White et al., *Nat. Chem.*, 2011, 3, 509–524). Most macrocyclization reactions show yields below 90% and the efficiencies often vary strongly depending on the peptide sequence and length. Chromatographic purification is also required to remove reagents and scavengers added for peptide release, as well as side chain protecting group byproducts generated during global deprotection.

It is evident from the above that there is an urgent need for novel methods, in particular methods that require less sophisticated steps of preparation for the generation of large peptide libraries or one or more peptides that can be added to peptide libraries, wherein the peptide libraries may then be screened for peptide therapeutics. This need is addressed by the present invention.

Summary

In one aspect, the present disclosure refers to method for preparing a library of peptides or an isolated peptide comprising
(a) releasing one or more linear dithiol peptides carrying a sulfhydryl group in the N-terminal region of the one or more peptides and being immobilized via a disulfide bridge in the C-terminal region of the one or more peptides on a solid phase from the solid phase by
(i) an agent reducing the disulfide bridge, thereby releasing the one or more linear dithiol peptides from the solid phase, wherein the agent is volatile and is removable by evaporation, or
(ii) a base that deprotonates the sulfhydryl group in the N-terminal region of the one or more linear dithiol peptides, thereby inducing an intramolecular disulfide exchange thereby releasing the one or more linear dithiol peptides from the solid phase in the form of one or more cyclic peptides.

Detailed Description

The present invention relates in a first aspect to a method for preparing a library of peptides or an isolated peptide comprising (a) releasing one or more linear dithiol peptides carrying a sulfhydryl group in the N-terminal region of the one or more peptides and being immobilized via a disulfide bridge in the C-terminal region of the one or more peptides on a solid phase from the solid phase by (i) an agent reducing the disulfide bridge, thereby releasing the one or more linear dithiol peptides from the solid phase, wherein the agent is volatile and can is removable by evaporation, or (ii) a base that deprotonates the sulfhydryl group in the N-terminal region of the one or more linear dithiol peptides, thereby inducing an intramolecular disulfide exchange thereby releasing the one or more linear dithiol peptides from the solid phase in the form of one or more cyclic peptides.

The term "comprise/comprising" is generally used in the sense of include/including, that is to say permitting the presence of one or more features or components. The terms "comprise" and "comprising" also encompass the more restricted terms "consist of" and "consisting of".

As used in the specification and claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

The term “peptide” as used herein refers to a polymer comprising at least one amino acid and at least one peptide bond. The peptide preferably comprises multiple - such as two or more, three or more, four or more, or five or more - amino acids. The peptide may also comprise non-amino acid building blocks and non-peptide linkages. Many of the peptides as described in the appended examples contain at their