Abstract

DNA-encoded peptide libraries are the basis for *in vitro* selection methods that use various biological systems (phage display; yeast display; mRNA display). Despite the great success of these selection methods, their obvious disadvantage is the limited number of building blocks, which consist of only twenty proteinogenic amino acids. The involvement of other non-proteinogenic amino acids and other building blocks could significantly expand the range of possible applications of these selection methods. For example, the introduction of chemical modifications in amino acid side chains in such libraries would allow the effective study of post-translational modifications (phosphorylation, acylation, glycosylation, methylation, etc.) in living organisms. The aim of this work was to develop a method for preparation of a fully synthetic DNA encoded library of peptides. The basic steps for the preparation were the chemical synthesis of the peptide and associated enzymatic synthesis of encoding DNA. Compatibility of chemical reactions with DNA is essential for the synthesis of DNA-encoded peptide libraries. Because the final acidic deprotection of the side chains in the peptide is not compatible with DNA, two approaches have been tested to overcome this problem. The first was an attempt to develop finer conditions for the deprotection of synthesized side chains that can be compatible with DNA. New, mild conditions for deprotection of BOC and *t*-Bu protecting groups were found. Unfortunately, other commonly used protecting groups have been resistant to this method. The second, new approach, which seemed to be productive, was the post-synthetic stabilization of the DNA tag itself against the condition of a strongly acidic environment by the introduction of 7-deaza purine nucleotides. In this way, a model DNA encoded peptide library construct was prepared and tested with a model proteases.

Key words: DNA-compatible reactions, DNA synthesis and amplification, DNA sequencing