2 The Aim of the Work

The aim of this work is the synthesis of unnatural amino acids and peptidomimetics in which these amino acids are incorporated and which consequently may be conformationally restricted. Hydrogen bonding in the synthesized compounds should be determined. These compounds also may show interesting biological activity and in the long run correlations between structure and biological activities of synthesized compounds should be investigated.

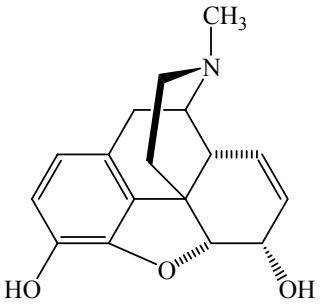
In our group in the last few years the multi-component reactions, namely Ugi-type condensations,[40] have been developed as a synthetic strategy for rapid and efficient generation of unnatural amino acids and compounds with amino acid-like backbones. Besides Ugi-type condensations, application of Gewald reaction for the synthesis of polysubstituted 2-aminothiophenes is also described in this work. In all these reactions 2-siloxycyclopropanecarboxylates served as starting material and as equivalents of functionalized carbonyl compounds.

This work describes the synthesis of compounds which may contribute to the development of novel peptidomimetics. A number of synthesized compounds can be regarded as unnatural δ-amino acids and dipeptide analogues (Scheme 18) which may be used for modifications of a peptide backbones as isosteric replacements and may be applied as components in the structure of more complex biologically active compounds. Furthermore, some of the synthesized compounds are promising building blocks for synthesis of highly stable unnatural oligomers and macrolactam natural product analogues, potential peptidomimetics and also molecules useful for studies of peptidomimetics and peptide recognition.

2.1 Peptidomimetics

There are different ways to develop a successful peptidomimetic. One generally applicable method involves synthesis of conformationally restricted low molecular mass analogues that imitate as closely as possible or block the function of a relatively large peptide at a receptor level. These analogues can be both peptide and nonpeptide compounds. The classic example of nonpeptide ligand which is a mimetic of endogenous peptide is morphine (**39**), which imitates the effect of, for example, β-endorphin (**40**) (an endogenous opioid composed of 31

amino acids). This example shows that it is possible, in principle, to use a small compound as a substitute for a relatively large peptide. Based on such discoveries, scientific efforts nowadays focus on the development of procedures for the controlled generation of a great variety of compounds which are promising peptidomimetics or are suitable for the examination of receptor binding.



39

Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-
Gln-Thr-Pro-Leu-Val-Thr-Phe-Lys-Asn-Ala-
Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Gly-Glu

40

Scheme 16. Morphine (**39**) and β-endorphin (**40**)

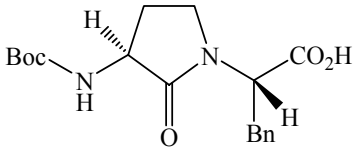
The active region of the endogenous peptides is relatively small and usually comprises a sequence of only a few amino acids. Structural modifications in this region lead to particularly pronounced changes in biological activity. These modifications involve: a) modifications of amino acids; b) synthesis of dipeptide analogues; c) modifications of a peptide backbones; d) global restriction of conformations; and e) imitations of secondary structures.

A dipeptide analogue is a molecule with limited conformative flexibility in comparison with that of the regular dipeptide. An isosteric replacement of an amide bond by a suitable mimetic is particularly important for the development of enzyme inhibitors[41, 42] because it provides proteolytic resistance to bioactive peptide sequences.

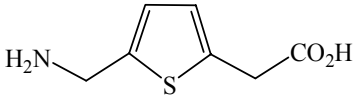
Global[43] restrictions in the conformation of a peptide are usually effected by limiting the flexibility of the peptide strand through cyclization. Lactams have been shown to be a particularly useful type of conformational constraints in peptides, like for example lactam-bridged dipeptide analogue **41**.[44]

Dipeptide mimetics may also be designed as “turn mimetics”, building blocks that forces a defined secondary structure after its incorporation into a peptide. Unnatural amino acids with

special properties such as rigidity, bulkiness or conformational constraints are of special interest as such building blocks. Turn mimetics not only restrict flexibility but can also change the accessible conformational space. One known example of turn mimetics is 5-aminomethyl-2-thiophene acetic acid (Ate) (**42**), developed by Feigel et al.[45]



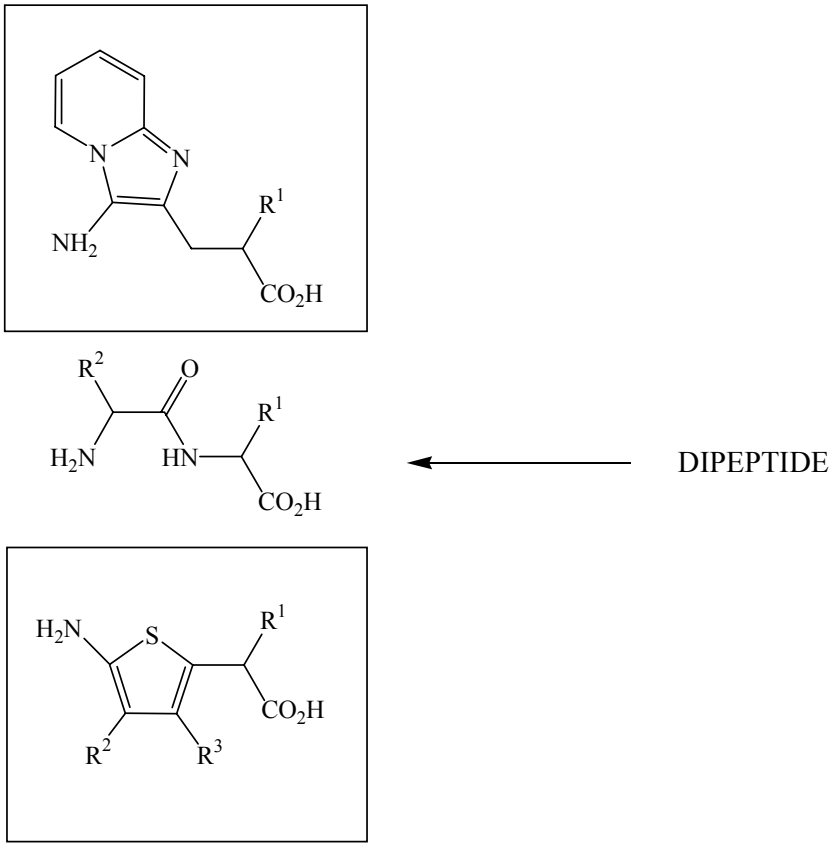
41



42

Scheme 17. Lactam-bridged dipeptide **41** and turn mimetic **42**

In this work I describe my attempts to prepare dipeptide analogues incorporating a pyridinoimidazolo moiety or a thiophene ring (Scheme 18). These new building blocks were used to synthesize new unnatural peptide-like compounds.



Scheme 18. Novel compounds incorporating a pyridinoimidazolo moiety or a thiophene ring as dipeptide analogues