Abstract

This thesis describes investigations towards proline-proline dipeptide mimetics with PPII-helix conformation. Based on molecular modelling studies from the "Forschungsinstitut für Molekulare Pharmakologie Berlin" (FMP), several heterotricyclic target structures were designed and their stereoselective synthesis was investigated. All three of them share structural features like a rigid helical geometry, a central carbonyl group which should act as a hydrogen bond acceptor, and a peptide-like structure which allows subsequent incorporation into peptides.

For the synthesis of the first target structure, *N*-Boc-*L*-serine was converted into a mono-protected chiral C_3-amino-diol. This was reacted with oxalic acid dimethyl ester to give a linear diamide which, then, could be cyclised to a bisoxazoline with functionalised side chains. Though, the further conversion into a tricycle and, thus, the synthesis of a peptide mimetic could not be achieved.

In a first attempt towards the synthesis of the second target structure, *N*-Boc-protected pyrrolidine derivatives were α-deprotonated using *sec*-butyl lithium and reacted with different electrophiles. Since this did not lead to promising results, a stepwise linear synthesis was developed. Having prepared an aldehyde from *L*-pyroglutamic acid and an alkyne from *L*-serine, the two building blocks were combined via cerium acetylide addition. After separation of the resulting diastereomers, the desired Felkin-Anh-product, which contained already all four required stereocenters, could be turned into a substituted bipyrrolidine structure. Unfortunately, this important key intermediate could not be further converted into the peptide mimetic.

The third target structure consists of two proline residues which are fixed in their relative PPII-conformation via an additional *cis*-configured olefin bridge. Therefore, a *cis*-5-vinyl proline and a *trans*-3-vinyl proline were stereoselectively synthesised and combined via peptide coupling. After ring closing metathesis and complete functionalisation, sufficient quantities of the peptide mimetic could be provided for biological investigations. At the FMP Berlin, several modified ligand peptides were synthesised using solid-phase supported standard techniques. Their binding affinity towards the VASP-EVH1-domain was investigated and turned out to be very promising. In all cases, a better binding interaction was observed compared with the native ligand peptides.