Abstract

There is a growing interest in the use of peptides as drugs due to their involvement in the regulation of many vital endogenous processes. Structurally, peptides consist of chains of amino acids which are connected via peptide (amide) bonds. However, peptide bonds cause problems in vivo since they (i) are sensitive to enzymatic cleavage and (ii) render peptides in general too hydrophilic for efficient membrane permeation.

In this study, the use of peptides as drugs was addressed by substituting the amide bonds to form more stable structures, so called peptidomimetics. More specifically, a way of transforming a tripeptide segment to a tripeptidomimetic was developed by the design of a 2,3,4-trisubstituted pyridine scaffold. First, the possibility of introducing amino acid moieties in the three positions of the pyridine scaffold was explored. A synthetic strategy was developed based on a 3-alkyl-2-fluoro-3-iodopyridine as a "functionalized scaffold", in which the side chain of the middle amino acid residue of a tripeptide is attached to the 3-position of the pyridine ring by reacting as electrophile in a halogen-dance reaction. The *N*-terminal amino acid moiety is attached to the 4-position of the functionalized scaffold as an *N*-protected α-amino aldehyde in a Grignard reaction, whereas the *C*-terminal amino acid moiety is attached to the 2-position of the scaffold as an α-hydroxy acid derived alkoxy nucleophile in an aromatic nucleophilic substitution reaction.

The synthetic strategy, which involves eight reaction steps, was used in the synthesis of six different tripeptidomimetics of Pro-Leu-Gly-NH_2 (PLG). PLG is a neuropeptide with the ability to potentiate the response of dopamine at the D2 receptors. The tripeptidomimetics were evaluated in the cell-based functional assay R-SAT. Four analogues with structural variations in the 3-position of the pyridine ring were found to be of similar potency as PLG. Interestingly, an analogue with a piperidine ring in the 4-position of the pyridine ring was significantly more potent than PLG. All pyridine based PLG mimetics produced similar bell-shaped dose-response curves as PLG, and none was active as dopamine agonist, which suggests that the peptidomimetics have a similar mechanism of action as the peptide. However, due to the defined planar geometry of the pyridine scaffold, these mimetics can not adopt a type II β-turn, which has been suggested to be the bioactive conformation of PLG in several studies. It is therefore speculated that there might be a second way in which PLG can interact with its modulatory site at the D2 receptors.

Keywords: peptidomimetic, trisubstituted pyridine, scaffold, halogen-dance, Grignard reaction, α-amino aldehyde, nucleophilic aromatic substitution, α-hydroxy acid, PLG, dopamine response, R-SAT functional assay.

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