**ANTIANGIOGENIC ACTIVITY AND PLASMA STABILITY**

**STUDY OF PEPTIDOMIMETICS CONTAINING**

**UNNATURAL PROLINE ANALOGS**

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Biologically active peptides are often considered as leading

compounds in the drugs development process. However,

the peptide bond is susceptible to enzymatic hydrolysis,

thus the peptides may not be entirely stable in body fluids.

One of the way to reduce this effect is to design new analogs

with modified structure and properties. In general, such compounds

are similar to the parent peptide sequence (to preserve

biological activity), but structural changes ensure higher

degradation resistance due to the enzyme failure of recognizing

cleavage site.

Angiogenesis is a fundamental process of forming new

capillaries from preexisting blood vessels. It is considered a

major factor in the development of tumors, their invasion and

metastasis. Vascular endothelial growth factor (VEGF165) is

one of the most potent proangiogenic factor. Recently, many

reports have suggested that neuropilin (NRP-1) may serve in

tumour cells as a separate receptor for VEGF165. These data

triggered interest in searching for new molecules interacting

with NPR-1 which would inhibit pathological angiogenesis

and could become prospective antiangiogenic and anti-tumour

drugs.

We have recently developed a peptide with the sequence

L(hR)PPR (*WO/2015/026251*) which exhibits a good inhibitory

effect on VEGF165/NRP-1 binding. The stability study

of this peptide indicated that the first enzymatic cleavage

occurs between prolines residues situated in the middle of

the peptide. This is probably due to the activity of dipeptidyl

peptidase IV, which catalyses the hydrolysis of the peptide

bond formed by the carboxyl group of proline located at position

2 of the chain. Therefore, to improve enzymatic stability

, peptidomimetics with the modified proline residue have

been designed. We have utilized following proline mimetics:

hydroxyproline, dehydroproline, octahydro-indole-2-carboxylic

acid and piperazine-2-yl acetic acid.

We report synthesis, stability in human plasma and inhibitory

effect on VEGF165/NRP-1 binding of obtained peptidomimetics.

They were synthesized via SPPS according to the

Fmoc-strategy and examined for the inhibitory activity by

enzyme-linked immunosorbent assay (ELISA). The stability

studies in human plasma were performed by ESI MS. The results

of structure-activity relationship study provide new insight

into structural requirements for inhibition of VEGF165/

NRP-1.

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