02 Homologs of Amino Acids and Explorations into the Worlds of β- and γ-Peptides

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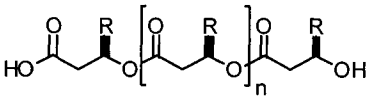
1 Introduction - From PHB to β-Peptides

In 1982 we have first become aware of the existence of the biopolymer PHB, consisting of (*R*)-3-hydroxybutanoates (HB), which we used as a source of readily available chiral building block for syntheses of natural products, such as elaiophylidin [1]. We then learned that short-chain PHB (*ca.* 150 HB units) is found in small amounts in all living cells and tissues, where it has been looked for (Figure 1), including plants, for instance



Microbial storage material (*s*-PHB), R = Me, n *ca.* 10^4
BIOPOL®, R = Me/Et, n *ca.* 10^4
PHB in genetically modified plants , R = Me, n *ca.* 10^4
cPHB (CaPPi complex; Ca-channel), R = Me, n *ca.* 150

E. Coli: inner cell membrane when genetically competent (caused by Ca^{2+})

Eukaryotic organisms: highest concentration in *mitochondria*
Ca^{2+} concentration mitochondrion/cytosol/extracellular
4 : 1 : 10^3

Human blood serum: 5-15 μg/ml, mainly bound to *albumin* which is **the** transport system for lipids and which is also binding *ca.* 40% of the serum Ca^{2+} content

Figure 1. The ubiquitous high- and low-molecular-weight biopolymer PHB is a microbial storage material (carbon and reductase equivalents, *cf.* Figure 2) and is found as part of ion-transporting systems in procaryotic and eucaryotic organisms, respectively [2].

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spinach or gorse. Another biopolymer with the same backbone structure is polymalic acid (PMA, up to 500 units long), found in molds and fungi in certain development stages of the organism and in certain compartments of the cells, in concentrations as high as 150g/l. PHB occurs in two varieties, as microbial storage material (sPHB, molecular weight up to 10^6 Da) and as short-chain, so-called complexing PHB (cPHB, chain lengths *ca.* 20-150 HB units). The metabolism (biosynthesis and degradation) of sPHB has been fully elucidated (Figure 2), while the biosynthetic origin of cPHB is unknown.

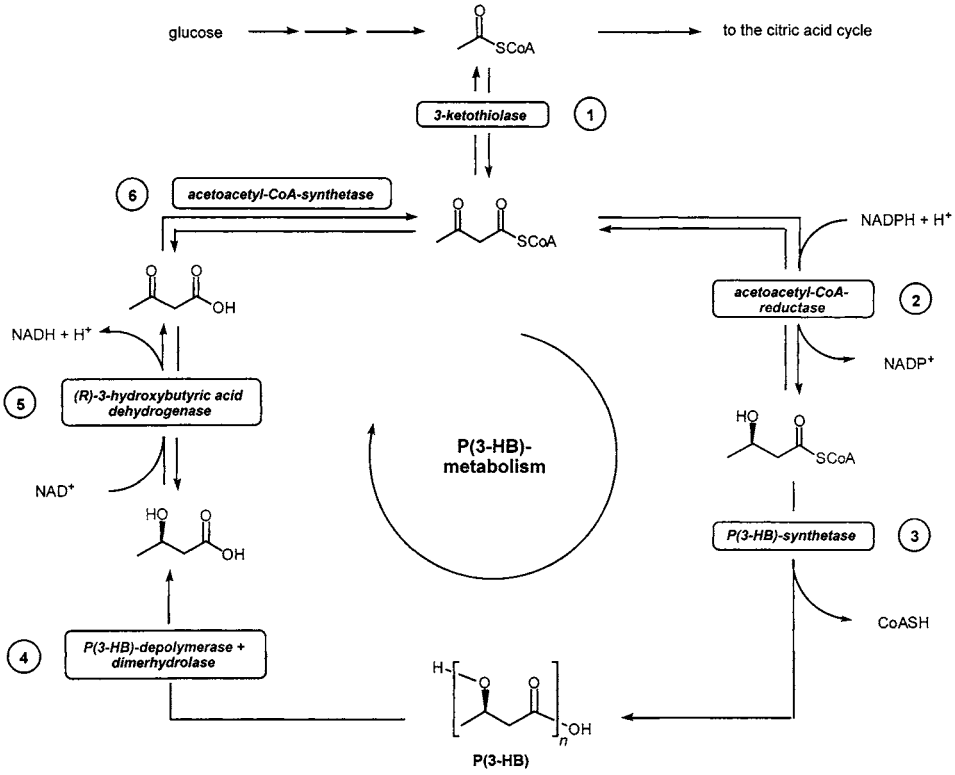

Figure 2. Biosynthesis and biodegradation of high-molecular-weight storage PHB (sPHB) by the most common mechanism. Microorganisms store PHB (acetate and NADH precursor!) as a survival measure, when glucose or other acetate precursors are available in the environment and when, at the same time, essential conditions for growth and multiplication are not met (*cf.* limitation of nitrogen, oxygen, phosphorous, trace element(s)) [2].

The function of PMA in DNA-polymerase regulation of the slime mold *Physarum polycephalum* has also been assigned (Figure 3). As chemists, we have been engaged in analyzing, synthesizing and studying structural and chemical properties of malic-acid and HB oligomers (OHBs) to help understand the various functions of these simple biopolymers with the (O-CHR-CH_2-CO) backbone. Many of the results obtained are collected in four review articles and a most recent paper [2] in which the seminal contributions by polymer chemists, biochemists, biologists, environmental scientists and medical

experts are referred to (a few names are *Dawes, Doi, Holler, Lemoign, Lenz, Marchessault, Reusch, Schlegel, Sinkey, Steinbüchel, Witholt*).

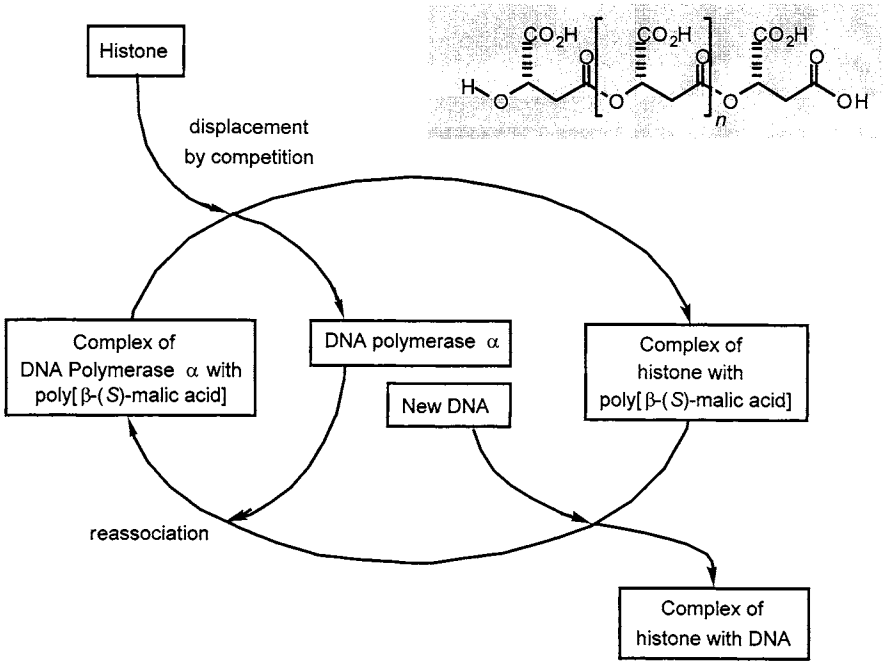

Figure 3. Proposed function of polymalate (PMA) in the reproduction of certain molds and fungi according to *E. Holler* (see references cited in [2]). Like DNA, PMA is an *anionic* polyelectrolyte, while the histones and DNA polymerase are proteins with high content of amino-acid residues carrying positively changed, *cationic* side chains (histidine, lysine, arginine).

In order to find out whether there is a preferred backbone conformation ("secondary structure") of OHBs and PHB in homogeneous solution or in phospholipid bilayers ("two-dimensional solvent") we have recently prepared derivatives labeled with various side chains, with isotopes, and with fluorescent groups for NMR and FRET measurements, to find that the polyester backbone is extremely flexible [3]; only in the crystal structures of cyclic HB derivatives (oligolides) did we see distinct folding patterns of the oligoester backbone [4] (Figure 4). One of these patterns resembled the 2_1 helix which had been identified in stretched fibers of sPHB, the other one was a 3_1 helix, the surface of which is covered with methyl groups. In the 3_1 helix all carbonyl groups are arranged parallel to the helix axis, with close proximity of the carbonyl oxygens in residue i and the chain-bound oxygens in residue (i+2) (Figure 4). Thus, it occurred to us that replacement of the latter by an NH should lead to hydrogen-bond formation and stabilization of the helix, so that one might to be able to observe it in solution. This was indeed the case, and our subsequent investigation of β-peptides has led to almost 70 papers since 1996, some of which are included in the list of references (with titles) [5-49].

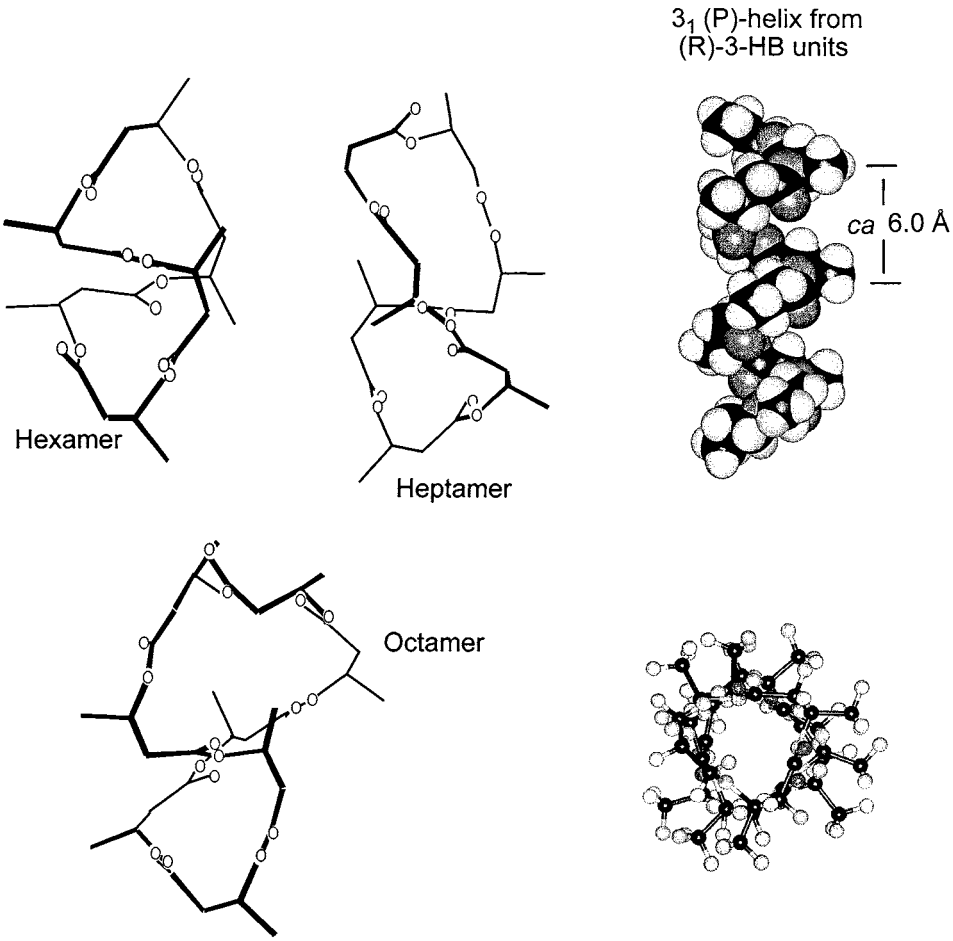

Figure 4. Folded and twisted conformations of (*R*)3-hydroxybutanoate oligolides (left) containing one (heptamer, octamer) or two (hexamer) single turns of a right-handed 3_1-helix, a model of which is shown on the right side in views from the side and along the helix axis. The helix is covered with methyl groups and has a dipole moment resulting from the unidirectional arrangement of the C=O bonds parallel to the helix axis [4].

2 β-and γ-Peptides – a Different World

General *formulae* of natural peptides (α) and of the unnatural β- and γ-peptides consisting of homologated α-amino acids are shown in Figure 5, in which an outline of the preparation of β- and γ- amino acids is also given. As can be seen, they are available by classical organic name reactions. The β^3- [50] and the γ^4-amino acid [51] derivatives are

prepared from the natural α-amino acid precursors, while for the β^2-analogs enantioselective routes to substituted succinic acid esters [34,52] or enantioselective *Mannich* reactions [12] have to be employed.

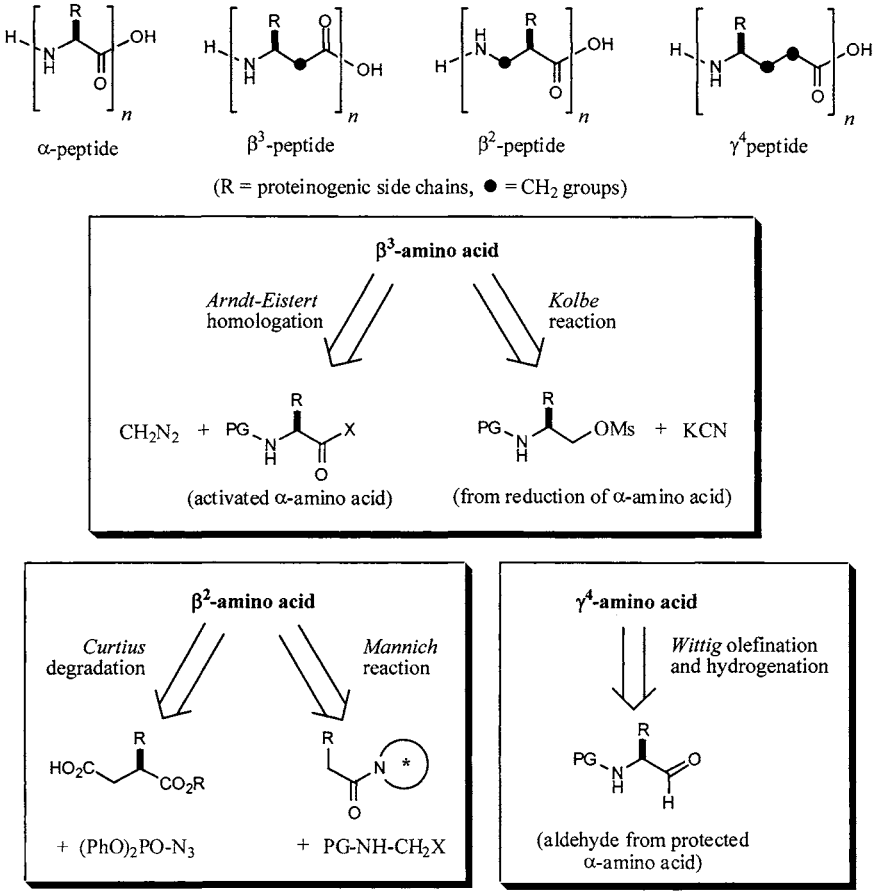

Figure 5. General structural *formulae* of the α-, β^3-, β^2- and γ^4-peptides derived from proteinogenic L-amino acids (top). Retrosynthetic presentation for the preparation of enantiopure building blocks required for the synthesis of β- and γ-peptides (bottom). – The oligomers (with n > 10 for α-, n = 6 for β- and n = 4 for γ-peptides) form helices in methanol solution; when we go from α- to β^3-to β^2- to γ^4-peptides the helicity is *P* (right-handed), *M* (left-handed), *P*, and *P*, respectively [12].

To our surprise, no oligomers of β-amino acids with the proteinogenic side chains had been synthesized up until 1995. Only polymers of high molecular weight (poly-β-lactams, mainly by industrial groups) and β-peptidic derivatives of the one and only proteinogenic β-amino acids, aspartic acid and asparagine (by a Spanish group [53]) had been described, and the effect of incorporation of single β-amino acid residues into α-peptidic chains had been studied (by medicinal chemists).

The assembly of the β- and γ-amino-acid building blocks to peptidic chains was achieved by simply using the established methods of peptide synthesis - in solution [6], on solid phase [11], or in a synthesizer machine [39]; also, the so-called "native ligation" can be applied with β-peptides [54]. Furthermore, the methods of analyzing and studying the structures of α-peptides and natural proteins can mostly be applied to β-peptides as well (the same is true for γ-peptides [51,55-60]). These methods are CD [35,37] and NMR [6, 49] spectroscopy, mass spectrometry [27,35], X-ray analysis [6,21,24,25,36], molecular dynamics (MD) calculations [9,13,18,31,38] and biological investigations [6, 15,20,26,30,41-43,45,46,48]. All of this sounds like routine, but the results are rather spectacular.

In the six years of research on peptides consisting of homologated proteinogenic amino acids we [5-52,54-59] and others [60-64] have embarked for a trip into an entirely new world, in which almost everything we know about α-peptides had to be disregarded. The homologous peptides form secondary structures, such as helices and turns, with as few as two to six residues [10,12,21,42,58], whereas α-peptides require more than ten residues for helix and turn formation under the same conditions (MeOH solution, NMR detection); parallel [6,21,64] and antiparallel [21,42,58] sheets and stacks (of cyclic β-peptides [8,22,36,45]) are found in solution and in the solid state (Figure 6). All of these secondary structures can be designed by choosing the "right" substitution pattern (constitution) and (relative and absolute) configuration of the residues in the β-and γ-peptidic chains, and MD calculations (GROMOS96 program, including solvent) furnish all the experimentally determined structures within a couple of nanoseconds ("*in silico*") [18,31,38]. Unlike natural α-peptide chains, which fold and unfold in a cooperative way, β-peptide folding is non-cooperative [19,49]. The shape, the handedness, the resulting dipole moments of sheets and helices are all different [65] as we go from α- to β- to γ-peptides, with increasing stability of the secondary structures in this order [44].

May be even more surprising than the structural properties of β-peptides are the results of their biological investigations [40,44]. (*i*) All the different types of β-and γ-peptides are absolutely stable to the peptide-cleaning enzymes [6,15,41] (Figure 7). (*ii*) One particular ^{14}C-labelled β-peptide was even metabolically stable in rats: samples collected for 96 hours from urine and feces, after *i.v.* administration, contained essentially no other radioactive compound but the β-peptide originally injected [66] (Figure 8). (*iii*) Even microorganisms in soil or in a sewer-water-treatment plant have difficulties growing on a simple β-tripeptide as sole carbon and nitrogen source [48]. (*iv*) Yet, β-and γ-peptidic hair-pin turns can be designed which are geometrically very similar to α-peptidic so-called "β-turns", often responsible for peptide-protein or protein interactions; thus, enzymatically stable β-peptidic peptidomimetics have been identified, for instance somatostatin analogs, consisting of as few as two β-amino-acid moieties and having sub-

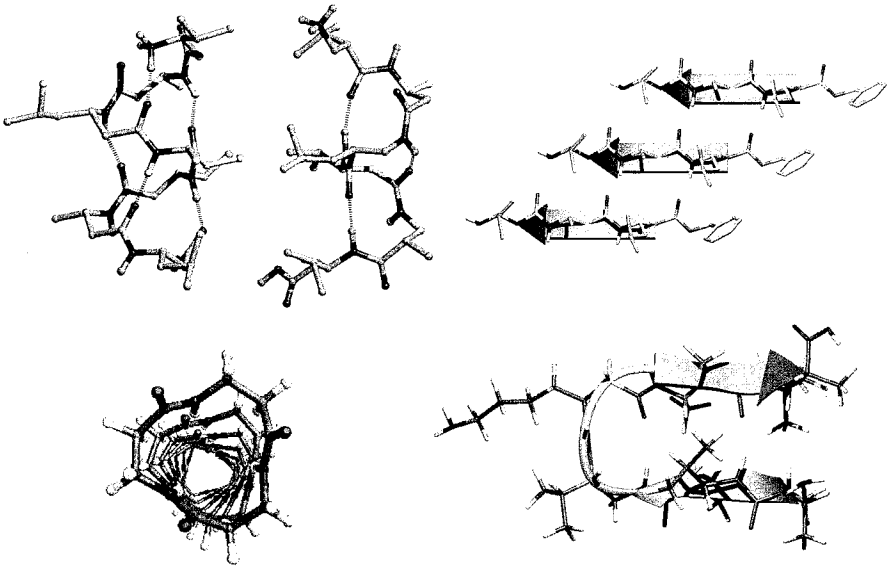

Figure 6. A 3_{14} and a 12/10 helix, a parallel and an antiparallel sheet (with hair-pin turn) and a stack (clockwise from top left) formed by β-peptides consisting exclusively of simple open-chain homologated α-amino-acid residues (Ala, Val, Leu, Lys side chains) and of α-Methyl-β-homo-Ala and Leu residues [12,21,36].

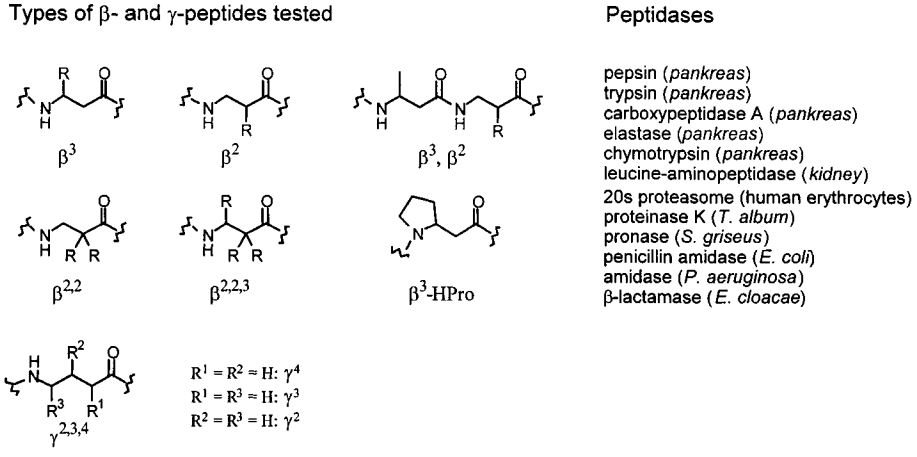

Figure 7. Complete proteolytic stability of all types of β-and γ-peptides towards a variety of peptidases. The β-peptides ranged in size from dimer to 15mer. The enzymes include all common types of peptidases (endo/exo, metallo, serine, threonine, and aspartyl proteases). After 40 hours there was no observable cleavage of any of the homologated peptides and no inhibition of the enzymes [41].

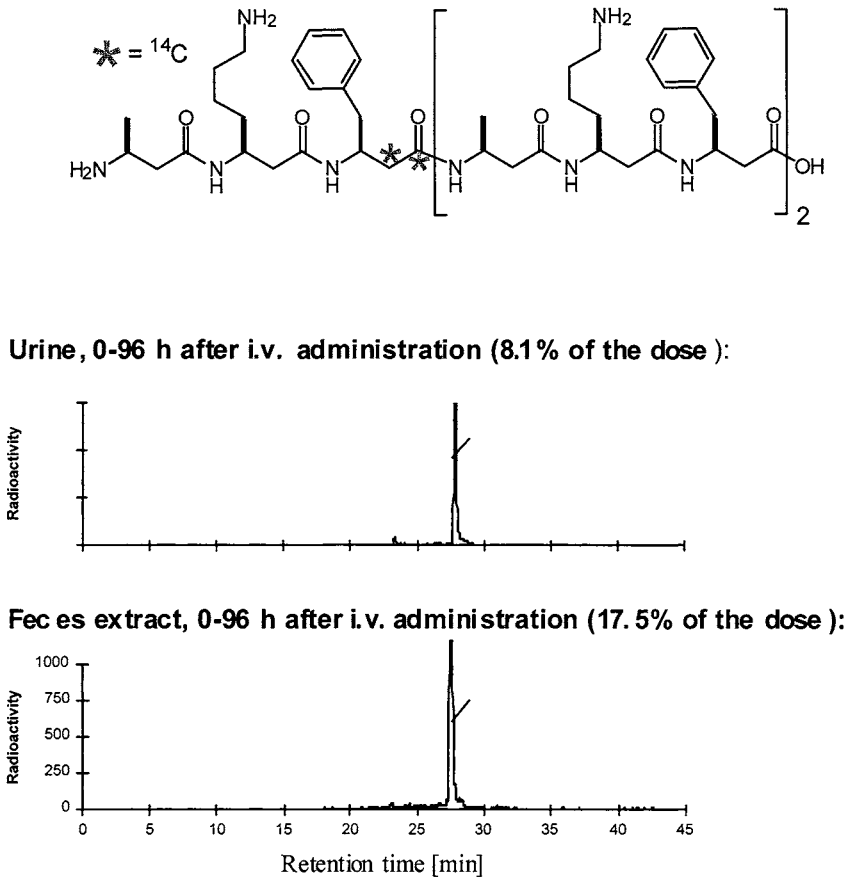

Figure 8. A β^3-nonapetide, which has been shown to be capable of mimicking an amphiphilic α-peptidic helical structure in a pepide-protein interaction [26], was ^{14}C-labelled and injected into rats. After 24 hours (in serum, not shown) and after 4 days (in urine and in feces the minor and major secretion pathways, respectively), there was hardly any metabolism, see the HPLC chromatograms with radiodetection (DSP01 is the compound, the formula of which is shown above) [68].

micromolar or even 10-20 nanomolar affinities to one of the five human receptors [20,30,42,46]. (*v*) Amphipathic helices of α-peptides, another motif for protein-protein binding, can be mimicked by β-peptidic helices, having polar and non-polar side chains positioned in the right manner [26]. (*vi*) The resistance to peptidases of β-peptides can be used to carry cargoes into cells; thus a fluorescence-labelled β-oligoarginine (a positive polyelectrolyte) is taken up by mammalian cells and migrates right to the cell nucleus docking to the *nucleoli* with their exposed DNA (a negative polyelectrolyte) [47,63]. (*vii*) Finally, antimicrobial [43,62], antiproliferative [45], but also hemolytic and cytotoxic [43,62] activities of the peptides consisting of homologated proteinogenic amino acids have been observed.

3 Conclusion

The simple idea at the outset of this research project, namely to replace an oxygen atom in a polyester chain by an NH group, has led to an almost explosive development of a new field, which is full of unexpected and promising results. For more details we refer to the list of references and to some review articles by us [10,40,44,50,65,67] and others [68-70], the latter ones also covering work on β-peptides consisting of or containing cyclic β-amino-acid residues, peptide analogs with N-N, N-O bonds or urea moieties incorporated in the backbone, or non-peptidic chains folding and turning.

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