Title: ACYLATED OLIGOPEPTIDES CONTAINING PHOSPHOTYROSINE AS INHIBITORS OF PROTEIN TYROSINE KINASES

Abstract

The invention relates to a compound of formula (I), wherein m is 2 to 15, X is arylcarbonyl, arylsulfonyl, cycloalkylcarbonyl, cycloalkanesulfonyl, heterocyclylcarbonyl or heterocyclicsulfonyl; A is absent or the bivalent radical of a natural or unnatural amino acid, B is the bivalent radical of a natural amino acid, PTI is the bivalent radical of phosphotyrosine or a phosphotyrosine mimic, AA stands for a bivalent radical of a natural or unnatural amino acid, and Y is hydroxy, a C-terminal protecting group or a primary, secondary or tertiary amino group, with the proviso that two or more sulfhydryl groups belonging to any amino acid A, B or AA are present as such or may form intramolecular disulfide bonds, or a salt thereof, said compound being useful for the treatment of diseases that respond to inhibition of the interaction of (a) protein(s) comprising (an) SH2 domain(s) and a protein tyrosine kinase or a modified version thereof.
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Acylated oligopeptides containing phosphotyrosine as inhibitors of protein tyrosine kinases

The present invention relates to a new class of pharmaceutically active compounds comprising an acylated peptide structure, processes for the preparation of said compounds, pharmaceutical preparations comprising said compounds, the compounds for the use in the therapeutic (including prophylactic) or diagnostic treatment of the animal or especially human body, and the use of said compounds for the therapeutic or diagnostic treatment of the animal or especially human body or for the manufacture of pharmaceutical preparations.

Background of the invention

Cancer and proliferative disorders affect a very large population and are one of the leading causes for death of human beings. A fundamental need exists to provide new classes of compounds for the treatment of these life-threatening and cumbersome diseases.

The process of signal transduction is responsible for relaying extracellular messages, e.g. chemical messages in the form of growth factors, hormones and neurotransmitters, via receptors, e.g. cell-surface receptors, to the interior of the cell. A central feature of these biochemical communication processes is the working of protein-tyrosine kinases. These enzymes, for example found as either transmembrane growth factor receptors or as cytosolic or nuclear non-receptor proteins, catalyze the phosphorylation of specific tyrosine residues. Examples for this class of enzymes include, but are not limited to, the PDGF receptor, the FGF receptor, the HGF receptor, members of the EGF receptor family such as the EGF receptor, erb-B2, erb-B3 and erb-B4, the src kinase family, Fak kinase and the Jak kinase family. The tyrosine-phosphorylated proteins are involved in the regulation of a range of metabolic processes, ranging from proliferation and growth to differentiation and metabolism control. Protein-tyrosine phosphorylation is known to be involved in modulating the activity of some special target enzymes as well as in initial and/or integral control of specific complex networks involved in signal transduction via various proteins containing a specific amino acid sequence called a Src Homology Region or SH2 domain (for review see
Proc. Natl. Acad. Sci. USA 90, 5891 (1990)). A malfunction in protein-tyrosine phosphorylation through tyrosine kinase overexpression or deregulation is causative for many oncogenic, degenerative and (hyper-)proliferative disorders such as cancer, inflammation, autoimmune disease, hyperproliferative skin disorders, such as psoriasis, and allergy/asthma.

Proteins comprising SH2 and/or SH3 domains that are effective in cellular signalling and transformation include, but are not limited to, the following: Src, Lck, Fps, ras GTPase-activating protein (GAP), phospholipase C, phosphoinositol-3 (PI-3) kinase, Fyn, Lyk, Fgr, Fes, ZAP-70, Sem-5, p85, SHPTP1, SHPTP2, corkscrew, Syk, Lyn, Yes, Hck, Dsrc, Tec, Atk/Bpk, Itk/Tsk, Arg, Csk, tensin, Vav, Emt, Grb2, BCR-Abl, Shc, Nck, Crk, CrkL, Syp, Blk, 113TF, 91TF, Tyk2, JAK1, and JAK2, especially Src, phospholipase C, phosphoinositol-3 (PI-3) kinase, Grb2, BCR-Abl, Shc, Nck, Crk and CrkL.

It has been possible to establish a direct link between activated receptor kinases and Ras with the finding that the mammalian Grb2 protein, a 26 kilodalton protein comprised of a single SH2 and two SH3 domains, directly couples receptor tyrosine kinases to the Ras guanine nucleotide exchange factor Sos in mammals and also Drosophila. The Grb2 SH2 domain binds to specific tyrosine phosphorylated sequences, e.g. in receptor tyrosine kinases, while the Grb2 SH3 domains bind to proline-rich sequences present in the Sos exchange factor.

The significance of ras-regulatory proteins in human tumors is also highlighted by the critical role of GRB2 in BCR-Abl mediated oncogenesis (J. Exp. Med., 179(1), 167-175 (1994)).

Recently, DNA sequences within the chromosomal locus 17q22-pter, which harbors the GRB2 gene, were shown by comparative genomic hybridization to exhibit a high frequency of amplification in both human breast cancer cell lines and tumors (Proc. Natl. Acad. Sci. USA 91, 2156-2160 (1994)).

In a study of GRB2 gene expression in human breast cancer cell lines, Northern Blot analysis also revealed that 7/19 breast cancer cell lines exhibited more than 2 fold overexpression of GRB2 mRNA relative to normal breast epithelial cells. In MCF-7, MDA-
MB-361, and 453 cells, the overexpression of GRB2 mRNA was accompanied by a 10-20 fold increase in the amount of GRB2 protein (Oncogene 9, 2723 (1994)).

SH2 domains are serving as recognition motifs for specific tyrosine-phosphorylated peptide sequences. Short, conserved motifs, primarily 3 to 6 amino acids on the carboxy-terminal side of a phosphotyrosine residue, carry the sequence-specific information for SH2 recognition. This concept has been supported by the mapping of separate sites for binding of SH2 domains from different signalling molecules on various receptors [see, e.g., Cell 69, 413 (1992); Proc. Natl. Acad. Sci. USA 89, 678 (1992); Mol. Cell. Biol. 12, 991 (1992); EMBO J. 11, 1365 (1992); EMBO J. 11, 559 (1992); EMBO J. 11, 3911 (1992); Cell 73, 321 (1993)]. Degenerate peptide libraries have also been used to predict the specificity of individual SH2 domains (src family members, Abl, Nck, Sem5, phospholipase C-γ, p85 subunit of PI-3 kinase, and HCP (amino terminal SH2) [see Cell 72, 767 (1993); Mol. Cell. Biol. 14, 2777 (1994)]. High-resolution crystallographic analysis and nuclear magnetic resonance of the SH2 domains of Src, Lck, PLC-γ C-terminal, p85 N-terminal, Abl, Syp C-terminal have also revealed that the region on the carboxyl side of the phospho-tyrosine carries the sequence-specific information for SH2 recognition. Each of these SH2 containing proteins controls a cellular pathway involved in the biological response to a growth factor. Activation of a particular pathway can thus be inhibited by designing a small molecule that specifically disrupts a phosphoprotein/SH2 domain interaction.

The approach of selectively eliminating a mitogenic pathway by a point mutation of the tyrosine kinase or a tyrosine-phosphorylated protein has been successful. For example, tyrosine 317 is the major site for SHC tyrosine phosphorylation and is the sole high-affinity binding site for Grb2 SH2. Mutant SHC proteins with substitution of tyrosine 317 by phenylalanine loose the capacity to be highly phosphorylated on tyrosine upon growth factor activation, to bind Grb2 and to induce neoplastic transformation [see Oncogene 9, 2827 (1994)]. A FGR receptor with a point mutation at tyrosine 766 does not bind phospholipase C-γ (an SH2-containing protein). It abolishes phosphatidylinositol turnover and calcium flux but not mitogenesis [see Nature 358, 678 (1992)]. For Epidermal Growth Factor Receptor (EGFR) it has been shown that tyrosine 1068 is the binding site for Grb2 SH2 (see Buday et al., Cell 73, 611-620 (1993)). A phosphopeptide based on the surrounding sequence, Pro-Val-Pro-Glu-Tyr(PO4)2-Ile-Asn-Gln-Ser, was shown to inhibit the interaction of phosphorylated EGFR and Grb2.
Uncoupling a tyrosine kinase from signal transduction pathways results therapeutically in antitumor activity. Antitumor activity for tyrosine kinase inhibitors has been demonstrated both in vitro and in vivo [see J. Antibiot. 39, 170 (1986); Eur. J. Cancer 26(6), 722 (1990); J. Med. Chem. 34, 2328 (1991); Cancer Res. 51, 4430 (1991); J. Med. Chem. 34, 2328 (1991); Helv. Chim. Acta 75, 696 (1992); Cancer Res. 52, 4492 (1992); Science 265, 1093 (1994); Science 267, 1782 (1995)]. For example, it has been shown that a small molecule called PD 153035 rapidly suppressed autophosphorylation of the EGF receptor at low concentrations in human epidermoid carcinoma cells and selectively blocked EGF-mediated cellular processes including mitogenesis, early gene expression and oncogenic transformation [see Science 265, 1093 (1994)]. In addition, it has been shown that tyrosine kinase inhibitors RS-13022 and 14620 supressed EGF-stimulated proliferation of HER-14 cells (transfected NIH 3T3 cells) and MH-85 cells in vitro. The MH-85 tumor is a human squamous cell carcinoma associated with three paraneoplastic syndromes: hypercalcemia, leukocytosis and cachexia. The well-characterized cells show overexpression of endogenous EGF receptor tyrosine kinase and are dependent on the EGF receptor signal transduction pathway for growth in vitro and in nude mice. In vivo, the compounds suppressed the growth of MH-85 tumors in nude mice as well as the expression of the paraneoplastic syndromes. An increase in life span of 75% was observed for RG-13022-treated tumor bearing mice [see Cancer Res. 51, 4430 (1991)]

4,5-Dianilinophthalimidines inhibit the growth of human tumor cells that overexpress EGFR or HER2-ErbB2 and exhibit good antitumor activity in mice in which these tumors are grown as xenografts (see Buchdunger et al., Proc. Natl. Acad. Sci USA 91, 2334 (1994) and Trinks et al., J. Med. Chem. 37, 1015 (1994)).

Immunologic downregulation of the p185<sup>Neu</sup> receptor in transgenic mice that express the rat neu oncogene (neuT) in mammary epithelial cells can also effectively prevent breast tumor development (Nature Medecine, 1(7), 1995).

Anilinoquinazolines also represent a class of compounds which exhibit promising anticancer activity. They were shown to inhibit the EGF-stimulated growth of human KB nasopharyngeal cells in vitro at concentrations of 1-10 μM.
By these results it can be shown that the inhibition of regulatory pathways by way of inhibition of protein tyrosine kinases results in therapeutically useful effects. It is therefore reasonable that inhibition at the level of interaction of protein tyrosine kinases with other proteins, such as those with SH2 domains, will result in similar therapeutic usefulness.

Not all phosphoproteins bind the same SH2-binding proteins. The divergent residues of individual domains are able to confer specificity for binding to structural variants within each ligand binding site [for SH2 domains, ligands with different amino acids surrounding the respective phosphotyrosine residue]. Various synthetic peptides derived from these ligand binding sites and as small as five amino acids in length have been shown to interfere specifically with these interactions in vitro [Mol. Cell. Biol. 11(2), 1125 (1991); Mol. Cell. Biol. 12(4), 1451 (1992); Cell 69, 413 (1992); and Cell 72, 767-778 (1993)].

It is a goal of the present invention to present small organic molecules that, due to their ability to mimic the structure of a phosphotyrosine peptide binding site, have the ability to disrupt the interaction between SH2 domains of (e.g. regulatory) proteins, for example that of Grb2, and proteins with phosphorylated moieties, especially phosphorylated tyrosine moieties, for example phosphorylated protein tyrosine kinase receptors. The effect is to inhibit the association of SH2 containing (e.g. regulatory) proteins with a protein tyrosine kinase in order to inhibit downstream signalling through one or more specifically targeted effector proteins.

Summary of the Invention

Surprisingly, it has been found that the compounds of the present invention show very favourable and valuable characteristics for pharmaceutical application, especially with regard to the therapeutic (including, in a broader sense, prophylactic) and/or diagnostic treatment of diseases that depend on the downstream signal transduction pathways, especially those mediated by an interaction of a protein comprising a SH2 domain with a tyrosine phosphorylated protein, such as a phosphorylated tyrosine protein kinase; proteins comprising one or more SH2 domains that are effective in cellular signalling and transformation include, but are not limited to, the following: Src, Lck, Fps, ras GTPase-activating protein (GAP), phospholipase C, phosphoinositol-3 (PI-3) kinase, Fyn, Lyk, Fgr, Fes, ZAP-70, Sem-5, p85, SHPTP1, SHPTP2, corkscrew, Syk, Lyn, Yes, Hck, Dsrc, Tec,
Atk/Bpk, Itk/Tsk, Arg, Csk, tensin, Vav, Emt, Grb2, BCR-Abl, Shc, Nck, Crk, CrkL, Syp, Blk, 113TF, 91TF, Tyk2, JAK1, and JAK2.

For example, very good inhibition is found in vitro with the compounds of formula I.

The new peptides of this invention preferably show selective inhibition of the binding of SH2-comprising proteins, such as Grb2, to phosphorylated proteins, especially activated growth factor receptor tyrosine kinases like EGF receptor tyrosine protein kinase, or Shc. The compounds of formula I disrupt the interaction between the SH2-comprising protein and the phosphoprotein, such as protein tyrosine kinase, and thus blocks the ability of the tyrosine protein kinases to initiate regulatory events depending on the SH2-comprising proteins, thus resulting in inhibition of specific downstream signal transduction pathways utilized in some hyperproliferative diseases, such as tumor diseases and psoriasis and the other diseases mentioned above and below, by uncoupling of the respective protein tyrosine kinase(s) from the respective SH2-containing effector protein.

One feature of the present invention is the positive effect of the moieties X as defined below on the inhibitory action of the compounds of the present invention on the interaction of a broad variety of phosphoproteins, especially phosphotyrosine-comprising proteins, to SH2-comprising proteins (e.g. those mentioned below in the definition of the bivalent radical -(AA)_m-). These moieties X are even able to allow for large sequence variability in the peptide derivatives of formula I.

Detailed description of the invention

The invention preferably relates to a an acylated peptide, namely a compound of the formula I,

\[ X - A - B - PTI - (AA)_m - Y \]  (I)

wherein
m is 2 to 15,

X is arylcarbonyl, arylsulfonyl, cycloalkylcarbonyl, cycloalkanesulfonyl, heterocyclylcarbonyl or heterocyclisulfonyl;

A is absent or the bivalent radical of a natural or unnatural amino acid,

B is the bivalent radical of a natural amino acid,

PTI is the bivalent radical of phosphotyrosine or a phosphotyrosine mimic,

AA stands for a bivalent radical of a natural or unnatural amino acid, and

Y is hydroxy, a C-terminal protecting group or a primary, secondary or tertiary amino group,

with the proviso that two or more sulfhydryl groups belonging to any amino acid A, B or AA are present as such or may form intramolecular disulfide bonds,

or a salt thereof.

Unless indicated otherwise, the general terms and names used in the description of the present invention preferably have the following meanings:

The term "lower" defines a moiety with up to and including maximally 7, especially up to and
including maximally 4, carbon atoms, said moiety being branched or straight-chained. Lower
alkyl, for example, is methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-
butyl, n-pentyl, n-hexyl or n-heptyl.

The compounds of formula I with one or more centers of asymmetry, such as one or more
asymmetric carbon atoms, may be present in the form of isomeric mixtures or pure isomers;
for example, a compound of formula I with one center of asymmetry may be present in the
form of a pure enantiomer or a mixture of enantiomers, e.g. a racemate, while a compound
of formula I with two or more centers of asymmetry may be present in the form of a pure
isomer (enantiomer) or in the form of diastereomeric mixtures, e.g. mixtures of epimers.
Generally, pure isomers of compounds of formula I are preferred over isomeric mixtures.

m is preferably 2 to 6, most preferably 2, 3 or 4.

Aryl has preferably from 6 to 14 ring carbon atoms, such as in phenyl (which is especially preferred), naphthyl (which is preferred), indenyl, indanyl, anthryl, phenanthryl, acenaphthyl or fluorenyl, and may be unsubstituted or preferably mono- to tri-substituted, especially by amino, mono- or di-lower alkylamino, lower alkanoylamino, such as acetylamino, amino-lower alkyl, mono- or di-loweralkylamino-lower alkyl, lower alkanoylamino-lower alkyl, lower alkanoylamino-lower alkyl, hydroxy, lower alkoxy, such as methoxy, carboxy, lower-alkoxycarbonyl, such as methoxycarbonyl, phenyl-, naphthyl- or fluorenyl-lower alkoxycarbonyl, such as benzyloxy-carbonyl, lower alkanoyl, cyano, lower alkyl, for example methyl, ethyl or propyl, halo-lower alkyl, for example trifluoromethyl, phenyl, 1- or 2-naphthyl, halogen, for example fluorine, chlorine or bromine, mercapto, lower-alkythio, such as methylthio, lower alkyl-sulfanyl, such as methylsulfanyl (CH$_3$-S(=O)-), sulfo, lower alkanesulfonfyl, for example methanesulfonfyl (CH$_3$-S(O)$_2$-), carbamoyl, mono- or di-lower alkylcarbamoyl, sulfamoyl, mono- or di-lower alkylaminosulfonfyl, and /or by nitro; more preferably mono- or di-substituted by a substituent selected independently from amino, mono- or di-lower alkylamino, lower alkanoylamino, such as acetylamino, amino-lower alkylamino, mono- or di-loweralkylamino-lower alkyl, lower alkanoylamino-lower alkyl, hydroxy, lower alkoxy, such as methoxy, carboxy, lower-alkoxycarbonyl, such as methoxycarbonyl, cyano, halogen, such as chloro or bromo, lower-alkythio, such as methylthio, and lower alkyl-sulfanyl, such as methylsulfanyl (CH$_3$-S(=O)-); most preferably mono- or disubstituted by amino.

Cycloalkyl preferably has from 3 to 10 ring carbon atoms, preferably from 4 to 7 carbon atoms, and is unsubstituted or preferably mono- to tri-substituted, especially by amino, mono- or di-lower alkylamino, lower alkanoylamino, such as acetylamino, amino-lower alkyl, mono- or di-loweralkylamino-lower alkyl, lower alkanoylamino-lower alkyl, hydroxy, lower alkoxy, such as methoxy, carboxy, lower-alkoxycarbonyl, such as methoxycarbonyl, phenyl-, naphthyl- or fluorenyl-lower alkoxycarbonyl, such as benzyloxy carbonyl, lower alkanoyl, cyano, lower alkyl, for example methyl, ethyl or propyl, halo-lower alkyl, for example trifluoromethyl, phenyl, 1- or 2-naphthyl, halogen, for example fluorine, chlorine or bromine, mercapto, lower-alkythio, such as methylthio, lower alkyl-sulfanyl, such as methylsulfanyl
(CH₂-S(=O)-), sulfo, lower alkanesulfonyl, for example methanesulfonyl (CH₃-S(O)₂-), carbamoyl, mono- or di-lower alky carbamoyl, sulfamoyl, mono- or di-lower alkylamino-sulfonyl, and/or by nitro; more preferably mono- or di-substituted by a substituent selected independently from amino, mono- or di-lower alkylamino, lower alkanoylamino, such as acetylamino, amino-lower alkylamino, mono- or di-lower alkanoylamino-lower alkyl, lower alkanoylamino-lower alkyl, hydroxy, lower alkoxy, such as methoxy, carboxy, lower-alkoxy carbonyl, such as methoxy carbonyl, cyano, halogen, such as chloro, lower-alkylthio, such as methythio, and lower alkyl-sulfanyl, such as methylsulfanyl (CH₃-S(=O)-); most preferably mono- or disubstituted by amino.

Heterocyclyl is preferably a single or double ring system having from 3 to 10 ring atoms, is bonded preferably via a carbon atom or also via a nitrogen atom and contains up to 3 hetero atoms selected from oxygen, sulfur, sulfur linked to 1 or 2 oxygen atoms and, most preferably, nitrogen; which in addition may also be fused with 1 or 2 phenyl radicals or with 1 or 2 cycloalkyl radicals, cycloalkyl preferably having from 5 to 7 ring atoms; and which may be unsaturated or partially or fully saturated, for example thienny, furyl, pyrrol, imidazolyl, such as imidazole-4-yl, pyrazolyl, oxazolyl, thiazolyl, such as 4- or 5-thiazolyl, tetrazolyl, pyridyl, such as pyridin-3- or pyridin-4-yl, pyrazinyl, such as pyrazin-2-yl, pyrimidinyl, pyridazinyl, indolyl, such as indole-2-yl, -3-yl or -5-yl, indoliny, such as indolin-2-yl, benzimidazolyl, such as 5-benzimidazolyl, quinolinyl, such as quinoline-8-yl, -6-yl, -4-yl, -3-yl or -2-yl, isoquinolyl, such as isoquinoline-1-yl, benzofuranyl, isobenzofuranyl, 2,3-dihydrobenzofuranyl, such as 2,3-dihydrobenzofuran-5-yl, chromanyl, cyclohexa[b]pyrrolyl, cyclohexa[b]pyridyl, cyclohexa[b]pyrazinyl, cyclohexa[b]pyrimidinyl, pyrrolidinyl, pyrrolylin, imidazolidyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, S,S-dioxo-thiomorpholinyl, 4,5,6,7-tetrahydroindolyl, 1,2,3,4-tetrahydroquinolyl or 1,2,3,4-tetrahydroisoquinolyl, with heterocyclyl, for example one of the last-mentioned radicals, being unsubstituted or substituted by one or more, preferably one or two, substituents independently selected from lower alkyl, for example methyl, phenyl, 1- or 2-naphthyl, phenyl-lower alkyl, for example benzyl, hydroxy-lower alkyl, for example hydroxymethyl or 2-hydroxyethyl, lower alkoxy, for example methoxy or ethoxy, amino, lower alkylamino, for example methyl-, ethyl- or tert-butyl-amino, di-lower alkylamino, for example dimethyl- or diethyl-amino, carboxy, lower alkoxy carbonyl, for example methoxy-, isopropoxy-, sec-butoxy- or tert-butoxy-carbonyl, phenyl- or naphthyl-lower alkoxy carbonyl, for example benzyl/alkoxy carbonyl, halogen, for example fluorine, chlorine, bromine or iodine, especially chlorine or bromine,
lower alkanoyl, for example acetyl or pivaloyl, nitro, oxo and cyano; more preferably heterocyclyl being selected from imidazolyl, such as imidazole-4-yl, thiazolyl, such as 4- or 5-thiazolyl, pyridyl, such as pyridin-3- or pyridin-4-yl, pyrazinyl, such as pyrazin-2-yl, indolyl, such as indole-2-yl, -3-yl or -5-yl, indoliny1, such as indolin-2-yl, benzimidazolyl, such as 5-benzimidazolyl, quinolinyl, such as quinoline-8-yl, -6-yl, -4-yl, -3-yl or -2-yl, isoquinolyl, such as isoquinoline-1-yl, and 2,3-dihydrobenzofuranyl, such as 2,3-dihydrobenzofuran-5-yl, these radicals being unsubstituted or substituted as above, most preferably from pyridyl, such as pyridin-3- or pyridin-4-yl, pyrazinyl, such as pyrazin-2-yl, indolyl, such as indole-2-yl, -3-yl or -5-yl, indoliny1, such as indolin-2-yl, quinolinyl, such as quinoline-8-yl, -6-yl, -4-yl, -3-yl or -2-yl, and isoquinolyl, such as isoquinoline-1-yl, these radicals being unsubstituted or substituted by amino.

In arylcarbonyl X, the aryl moiety is preferably defined as above; more preferably, arylcarbonyl is selected from benzoyl, 1-naphthoyl, 2-naphthoyl and, even more preferably, from benzoyl substituted with amino; lower alkylamino; amino-lower alkyl; hydroxy; lower alkoxy; amino and hydroxy; amino and lower alkoxy; carboxy; lower-alkoxycarbonyl; cyano; halogen, especially chloro; lower-alkythio; or lower alkylsulfinyl, and from 1- or 2-naphthoyl substituted with amino; especially from 4-aminobenzoyl, 3-aminobenzoyl (more preferred), 2-aminobenzoyl (most preferred); 3,5-diaminobenzoyl; 4-lower alkylamino-benzoyl, such as 4-methylamino-benzoyl, 4-(amino-lower alkyl)-benzoyl, such as 4-(methylamino)-benzoyl, 4-hydroxy-benzoyl, 2-hydroxybenzoyl, 4-lower alkoxy-; such as 4-methoxybenzoyl, 4-amino-2-hydroxy-benzoyl, 4-amino-3-lower alkoxy-benzoyl, such as 4-amino-3-methoxy-benzoyl, 4-carboxybenzoyl, 4-lower alkoxy-carbonyl-benzoyl, such as 4-methoxy-carbonyl-benzoyl, 4-cyanobenzoyl, 4-lower alkylthio-benzoyl, such as 4-methylthiobenzoyl, 4-lower alkylsulfinyl-benzoyl, such as 4-lower methylsulfinyl-benzoyl and aminonaphthoyl, such as 3-amino-2-naphthoyl; and most preferably from 4-aminobenzoyl, 3-aminobenzoyl (more preferred), 2-aminobenzoyl (most preferred); 3,5-diaminobenzoyl; 2-hydroxybenzoyl, 4-lower alkoxy-; such as 4-methoxybenzoyl, and 3-amino-2-naphthoyl.

In arylsulfonyl X [= aryl-S((O)2)-] , the aryl moiety is preferably defined as above; more preferably, arylsulfonyl is 1-or 2-naphthalenesulfonyl which is substituted with amino or mono- or di-lower alkylamino, such as dimethylamino; especially 5-dimethylamino-naphthalene-1-sulfonyl.
In cycloalkylicarbonyl X, cycloalkyl is preferably as defined above; more preferably, cycloalkylicarbonyl is C₃-C₇, especially C₄- C₅- or C₆-cycloalkylicarbonyl, such as cyclohexylicarbonyl, and is unsubstituted or substituted by amino; most preferably 1-amino-cyclohexylicarbonyl or 1-amino-cyclopentylcarbonyl.

In cycloalkanesulfonyl X, cycloalkyl is preferably as defined above; more preferably, cycloalkanesulfonyl is C₃-C₇-cycloalkanesulfonyl which is unsubstituted or preferably substituted with amino.

In heterocyclylicarbonyl, the heterocycly moiety is preferably as defined above; more preferably, heterocyclylicarbonyl is selected from pyridylcarbonyl which is unsubstituted or substituted with amino, such as pyridin-4-yl- or pyridin-3-ylcarbonyl, or amino-pyridin-3-ylcarbonyl, such as 2- or 6-amino-pyridin-3-ylcarbonyl; pyrazinyl, such as pyrazin-2-yl, which is unsubstituted or substituted with amino, such as in 3-amino-pyrazin-2-ylcarbonyl, quinolinyl-carbonyl, such as quinoline-2-, quinoline-3-, quinoline-4- or quinoline-8-ylcarbonyl, isoquinolyl, such as isoquinoline-1-yl, indolylcarbonyl, such as indole-5-yl-, indolyl-3-yl- or indole-2-yl-carbonyl; and indolylcarbonyl, such as indolin-2-ylcarbonyl, the latter being especially preferred.

In heterocyclylsulfonyl X [= heterocycly-S((O)₂)-], the heterocycly moiety is preferably as defined above; more preferably, heterocyclylsulfonyl is quinolinylsulfonyl, such as quinoline-8-ylsulfonyl.

A is absent or the bivalent radical of a natural or unnatural amio acid as defined below for AA.

B is the bivalent radical of a natural amino acid as defined below for AA. Preferably, B is an amino acid other than the moiety of the formula.
wherein K and L are independently H or methyl and \( p \) is 1 or 2, such as histidine.

Preferably, the bivalent radical \(-A-B-\) in formula I is an analogue of an SH2 domain binding site of a protein with phosphotyrosine of a mammal, especially a human, for example one of the binding sites mentioned in Songyang et al., Cell 72, 767-778 (1993), e.g. (i) in the case of the Src family SH2 binding proteins, especially an analogue of the human CD3 \( \gamma \) chain preceding Tyr 110 (that is, -Gly-Leu-) or Tyr 122 (that is, -Glu-Ala-), an analogue of the human Rb-associated rb 110 chain preceding Tyr 321 (that is, -Lys-Arg-), an analogue of the human vav oncogene chain preceding Tyr 126 (that is, -Glu-Ile-), an analogue of the human ErbB3 chain preceding Tyr 1270 (that is, -Gln-Gly-), an analogue of the human T cell CD7 chain preceding Tyr 222 (that is, -Val-Val-) or an analogue of the human G2 cyclin b chain preceding Tyr 255 (that is, -Ser-Lys-), (ii) in the case of the Abl SH2 binding proteins, especially an analogue of the human B cell CD19 chain preceding Tyr 409 (that is, -Glu-Gly-) or Tyr 439 (that is, -Ser-Gly-), an analogue of the human B cell CD 72 chain preceding Tyr 39 (that is, -Ile-Thr-), an analogue of the human colony-stimulating factor 1 receptor chain preceding Tyr 923 (that is, -Arg-Asp-), an analogue of the human JunB chain preceding Tyr 182 (that is, -Pro-Val-), an analogue of the human protein kinase C \( \beta \)-1 chain preceding Tyr 662 (that is, -Phe-Ser-), (iii) in the case of Crk SH2 binding proteins, especially an analogue of the human Fer tyrosine kinase chain preceding Tyr 615 (that is, -Lys-Gln-), (iv) in the case of Nck SH2 binding proteins, especially an analogue of the human cell cycle gene 1 protein chain preceding Tyr 139 (that is, -Ser-Asp-), (v) in the case of Sem-5/Grb2 SH2 binding proteins, especially an analogue of the human EGF receptor chain preceding Tyr 1092 (that is, -Pro-Glu-), an analogue of the human EGF receptor chain preceding Tyr 1138 (that is, -Pro-Glu-), an analogue of the human SHC chain preceding Tyr 317 (that is, -Pro-Ser-), an analogue of the human HGF receptor chain preceding Tyr 1374 (that is, -Ala-Thr-), an analogue of the human ErbB2 chain preceding Tyr 1139 (that is, -Pro-Glu-), an analogue of the human ErbB3 chain preceding Tyr 1200 (that is, -Tyr-Glu-) or Tyr 1262 (that is, -Tyr-Glu-), an analogue of the human IGF-1 receptor chain preceding Tyr
1125 (that is, -Met-Ala-), an analogue of the human Fit tyrosine kinase chain preceding Tyr 1213 (that is, -Val-Arg-), an analogue of the human insulin receptor chain preceding Tyr 1149 (that is, -Met-Ala-), an analogue of the human CD45 PTPase chain preceding Tyr 706 (that is, -Ser-Asn-), or Tyr 1015 (that is, -Ser-Lys-), (vi) in the case of p85 N-terminal SH2, especially an analogue of the human PDGF receptor β chain preceding Tyr 740 (that is, -Gly-Gly-) or Tyr 751 (that is, -Val-Asp-), an analogue of the human c-Kit chain preceding Tyr 721 (that is, -Asn-Glu-), an analogue of the human ErbB3 chain preceding Tyr 1257 (that is, -Gly-Asp-), Tyr 1270 (that is, -Gln-Gly-), Tyr 1241 (that is, -Glu-Asp-), Tyr 1257 (that is, -Gly-Asp-), Tyr 922 (that is, -Asp-Val-), Tyr 1035 (that is, -Ser-Gly-), Tyr 1178 (that is, -Glu-Glu-), or Tyr 1203 ( -Leu-Gly-), (vii) in the case of p85 C-terminal SH2, especially the same sites as for p85 N-terminal SH2, (vii) in the case of PLC-γ C-terminal SH2, especially an analogue of the human PDGF receptor β chain preceding Tyr 1021 (that is, -Asn-Asp-), an analogue of the human PDGF receptor α chain preceding Tyr 1018 (that is, -Ser-Gly-), an analogue of the human ErbB2 chain preceding Tyr 1127 (that is, -Asp-Gly-), (viii) in the case of PLC-γ N-terminal SH2 binding proteins, especially an analogue of the human basic FGF receptor I, II, II, IV chain preceding -Tyr 766 (that is, -X-Glu-), an analogue of the human EGF receptor chain preceding Tyr 978 (that is, -Gln-Arg-) or Tyr 1197 (that is, -Ala-Glu-), an analogue of the human ErbB2 chain preceding Tyr 1248 (that is, -Pro-Glu-), and (ix) in the case of SHPTP2 N-terminal SH2 binding proteins, especially an analogue of the human PDGF receptor β chain preceding Tyr 1009 (that is, -Val-Leu-) or Tyr 1021 (that is, -Asn-Asp-), an analogue of the human PDGF receptor α chain preceding Tyr 1018 (that is, -Ser-Gly-), Tyr 988 (that is, -Asn-Ala-) or Tyr 720 (that is, -Arg-Ser-), an analogue of the human ErbB3 chain preceding Tyr 1159 (that is, -Asn-Gly-) or Tyr 471 (that is, -Pro-Leu-), an analogue of the human Fit receptor type tyrosine kinase chain preceding Tyr 1169 (that is, -Lys-Asp-), an analogue of the human Kit receptor type tyrosine kinase chain preceding Tyr 568 (that is, -Asn-Asn-), an analogue of the human Ros receptor type tyrosine kinase chain preceding Tyr 234 (that is, -Pro-Gln-), an analogue of the human HGF receptor (Met) chain preceding Tyr 1367 (that is, -Glu-His-) or Tyr 1374 (that is, -Ala-Thr-);

and (x) most especially an analogue of the Epidermal Growth Factor Receptor (EGFR) sequence preceding Tyr 1068, the binding site for Grb2 SH2 (see Buday et al., Cell 73, 611-620 (1993)), that is the sequence -Pro-Glu-; wherein in each case one or both amino acids are replaced by other natural or unnatural amino acids as defined above which still
allow for binding to the respective SH2-comprising protein, especially Grb2, most preferably A being absent and B being an analogue of an unnatural or natural amino acid as described above, especially one of those mentioned under (i) to (x) in the N-terminal position of the mentioned dipeptide radicals.

A is especially the bivalent radical of the amino acid proline which may be present in the D-, (D,L)- or preferably L-form or most preferably absent (that is, X is directly bound to B).

B is more preferably a bivalent radical of an amino acid selected from proline, S-protected cysteine, especially S-acetamidomethyl-cysteine, asparagine, β-alanine; and, more preferably, glutamic acid, cysteine that forms a disulfide bond with a further cysteine AA, glycine, alanine, valine, leucine and isoleucine; any of which is present in the (D,L)- or preferably the D- or (most preferably) the L-form.

For PTI, a bivalent radical of phosphotyrosine is especially (D,L), (D)- or preferably (L)-4-(O-Phosphono)-Tyr [= (O-PO₃H₂)Tyr] (bound N-terminally via the imino group resulting from the α-amino group and C-terminally via the carbonyl group resulting from its α-carboxy group), preferably the radical of the formula A

![Chemical structure](image)

\[ \text{(A).} \]

A bivalent radical of a phosphotyrosine mimic PTI is defined as any radical that is able to replace a phosphotyrosine radical which resembles, but is structurally different from the respective phosphotyrosine radical and which cannot lose its phosphono-group too easily due to hydrolysis. Preferably, such a mimic is selected from the respective bivalent radical (which is bound N-terminally via the imino group resulting from the α-amino group and C-terminally via the carbonyl group resulting from its α-carboxy group) of an amino acid.
selected from phosphonomethyl-phenylalanine, especially 4-phosphonomethyl-phenylalanine, phosphono-(α-fluoro)methyl-phenylalanine, especially 4-phosphono-(α-fluoro)methyl-phenylalanine, phosphono-(α,α-difluoro)methyl-phenylalanine, especially 4-phosphono-(α,α-difluoro)methyl-phenylalanine, phosphono-(α-hydroxy)methyl-phenylalanine, especially 4-phosphono-(α-hydroxy)methyl-phenylalanine, O-sulfo-tyrosine, such as 4-(O-sulfo)tyrosine, dicarboxymethoxy-phenylalanine (= (HOOC)$_2$CH$_2$O-phenylalanine), especially p-(dicarboxymethoxy)-phenylalanine; (less preferably) phosphonophenylalanine, such as 4-phosphonophenylalanine; aspartic acid, glutamic acid, phosphoserine and phosphothreonine, each of which is present in the (D,L)-, D- or preferably the L-form.

For PTI, a bivalent radical of phosphotyrosine and especially a bivalent radical of phosphono-(α,α-difluoro)methyl-phenylalanine, especially 4-phosphono-(α,α-difluoro)methyl-phenylalanine is especially preferred.

AA stands for a natural or unnatural amino acid, and is preferably a bivalent radical of an α- or β-amino acid which is preferably bonded N-terminally by way of its α- or β-amino group and C-terminally by way of its carboxy group and is preferably selected from the group comprising a bivalent radical of a natural α- amino acid having the L-configuration, such as those normally occurring in proteins, or an epimer of such an amino acid, that is to say having the unnatural D-configuration, or a (D,L)-isomeric mixture thereof; or a homologue of such an amino acid, for example a β-amino acid or an α-amino acid wherein the amino acid side chain has been shortened by one or two methylene groups or lengthened to up to 10 carbon atoms, such as an α-amino alkanoic acid with 5 up to and including 10 carbon atoms in a linear chain, a substituted aromatic (α-aryl or α-aryl lower alkyl) amino acid wherein the aryl radical has from 6 to 14 carbon atoms, for example a substituted phenylalanine or phenylglycine wherein the phenyl may be mono- or poly-substituted by lower alkyl, for example methyl, lower alkoxy, for example methoxy, lower alkanoyloxy, for example acetoxy, amino, lower alkylamino, for example methylamino, di-lower alkylamino, for example dimethylamino, lower alkanoylamino, for example acetylamino or pivaloylamino, lower alkoxy carbonylamino, for example tert-butoxycarbonylamino, arylmethoxy-carbonylamino wherein aryl preferably has from 6 to 14 carbon atoms, for example
benzyloxy carbonylamino or 9-fluorenylmethoxy carbonylamino, halogen, for example fluorine, chlorine, bromine or iodine, carboxy and/or by nitro, a benzo-fused phenylalanine or phenylglycine, such as α-naphthylalanine, and a hydrogenated phenylalanine or phenylglycine, such as cyclohexylalanine or cyclohexylglycine, or an α-amino heterocyclic-lower alkanoic acid wherein heterocyclyl preferably is a single or double ring system having from 3 to 10 ring atoms, is bonded via a carbon atom or via a nitrogen atom and contains up to 3 further hetero atoms selected from oxygen, nitrogen, sulfur, and sulfur linked to 1 or 2 oxygen atoms, and may be unsaturated or partially or fully saturated, for example furyl, pyrrolyl, pyrrolidinyl, morpholinyl, pyridyl or indolyl, a cyclic α-amino-(α,α-lower alkylene)-carbonic acid or an α-amino-[[(C₉-C₁₂)-bicyclo]-carbonic acid; each being present in the L-, D- or (D,L)-configuration and in unprotected or amino-, carboxy- or sulfhydryl-protected form.

Especially preferred is the bivalent radical, bonded via its α-amino and its α- or β-carbonyl group, of an amino acid selected from glycine (H-Gly-OH), alanine (H-Ala-OH), β-alanine (H-βAla-OH), valine (H-Val-OH), norvaline (α-aminovaleric acid), leucine (H-Leu-OH), isoleucine (H-Ile-OH), norleucine (α-aminohexanoic acid, H-Nle-OH), α-amino-n-decanoic acid, serine (H-Ser-OH), homoserine (α-amino-γ-hydroxybutyric acid), threonine (H-Thr-OH), methionine (H-Met-OH), cysteine (H-Cys-OH), S-acetylaminoethyl-cysteine (H-Cys(Acm)-OH), proline (H-Pro-OH), trans-3- and trans-4-hydroxyproline, phenylalanine (H-Phe-OH), tyrosine (H-Tyr-OH), 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenylserine (β-hydroxyphenylalanine), phenylglycine, α-naphthylalanine (H-Nal-OH), cyclohexyl alanine (H-Cha-OH), cyclohexylglycine, tryptophan (H-Trp-OH), indole-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aspartic acid (H-Asp-OH), asparagine (H-Asn-OH), aminomalonic acid, aminomalonic acid monoamide, glutamic acid (H-Glu-OH), glutamine (H-Gln-OH), histidine (H-His-OH), arginine (H-Arg-OH), lysine (H-Lys-OH), N′-benzyl-N′-methyl-lysine, N,N′-dibenzyl-lysine, δ-hydroxylysine, ornithine (α,δ-diaminovaleric acid), α-amino-cyclopentane carboxylic acid (H-Ac₅c-OH), α-amino-cyclohexane carboxylic acid (H-Ac₆c-OH), α-amino cycloheptane carboxylic acid, α-(2-amino-2-norbornane)-carboxylic acid, α,γ-diaminobutyric acid and α,β-diaminopropionic acid; it being possible for each of the mentioned amino acids (with the exception of glycine or any other amino acid without asymmetric carbon atom) to be in the D-, L- or (D,L)-form, preferably in the L- or in the D-form.
More preferably, the bivalent radical -(AA)_n- in formula I is an analogue of an SH2 domain binding site of a protein with phosphotyrosine of a mammal, especially a human, for example one of the binding sites mentioned in Songyang et al., Cell 72; 767-778 (1993), e.g. (i) in the case of the Src family SH2 binding proteins, especially an analogue of the human CD3 ε chain following Tyr 110 (that is, -Asn-Glu-Leu-Gln-Lys-Asp-Arg-Met-Ala-Glu-Ala-) or Tyr 122 (that is, -Ser-Glu-Ile-Gly-Met-), an analogue of the human Rb-associated rb 110 chain following Tyr 321 (that is, -Glu-Glu-Ile-Tyr-Leu-), an analogue of the human vav oncogene chain following Tyr 126 (that is, -Glu-Asp-Leu-Met-Arg-), an analogue of the human ErbB3 chain following Tyr 1270 (that is, -Glu-Glu-Met-Arg-Ala-), an analogue of the human T cell CD7 chain following Tyr 222 (that is, -Glu-Asp-Met-Ser-His-) or an analogue of the human G2 cyclin b chain following Tyr 255 (that is, -Glu-Asp-Met-Ser-His-), (ii) in the case of the Abl SH2 binding proteins, especially an analogue of the human B cell CD19 chain following Tyr 409 (that is, -Glu-Glu-Pro-Asp-Ser-) or Tyr 439 (that is, -Glu-Asn-Pro-Glu-Asp-), an analogue of the human B cell CD72 chain following Tyr 39 (that is, -Glu-Asn-Val-Gln-Val-), an analogue of the human colony-stimulating factor 1 receptor chain following Tyr 923 (that is, -Thr-Asn-Leu-Pro-Ser-), an analogue of the human JunB chain following Tyr 182 (that is, -Thr-Asn-Leu-Ser-Ser-), an analogue of the human protein kinase C β-1 chain following Tyr 662 (that is, -Thr-Asn-Pro-Glu-Phe-), (iii) in the case of Crk SH2 binding proteins, especially an analogue of the human Fcr tyrosine kinase chain following Tyr 615 (that is, -Asp-His-Pro-Asn-Ile-), (iv) in the case of Nck SH2 binding proteins, especially an analogue of the human cyclase gene 1 protein chain following Tyr 139 (that is, -Asp-Glu-Asp-Asp-Tyr-), (v) in the case of Sem-5/Grb2 SH2 binding proteins, especially an analogue of the human EGF receptor chain following Tyr 1092 (that is, -Ile-Asn-Gln-Ser-Val-), an analogue of the human EGF receptor chain following Tyr 1138 (that is, -Leu-Asn-Thr-Val-Gln-), an analogue of the human SHC chain following Tyr 317 (that is, -Val-Asn-Val-Gln-Asn, an analogue of the human HGF receptor chain following Tyr 1374 (that is, -Val-Asn-Val-Leu-Arg-Asn), an analogue of the human ErbB2 chain following Tyr 1139 (that is, -Val-Asn-Gln-Pro-Asp-), an analogue of the human ErbB3 chain following Tyr 1200 (that is, -Met-Asn-Arg-Arg-Arg-) or Tyr 1262 (that is, -Met-Asn-Arg-Gln-Arg-), an analogue of the human IGF-1 receptor chain following Tyr 1125 (that is, -Leu-Asn-Ala-Asn-Lys-), an analogue of the human Fit tyrosine kinase chain following Tyr 1213 (that is, -Val-Asn-Ala-Phe-Lys-), an analogue of the human insulin receptor chain following Tyr 1149 (that is, -Leu-Asn-Ala-Lys-)
Lys), an analogue of the human CD45 PTPase chain following Tyr 706 (that is, Ile-Asn-Ala-Ser-Tyr), or Tyr 1015 (that is, Ile-Asn-Ala-Ser-Phe), (vi) in the case of p85 N-terminal SH2, especially an analogue of the human PDGF receptor β chain following Tyr 740 (that is, Met-Asp-Met-Ser-Lys-Asp-Glu-Ser-Val-Asp) or Tyr 751 (that is, Val-Pro-Met-Leu-Asp), an analogue of the human c-Kit chain following Tyr 721 (that is, Met-Asp-Met-Lys-Pro), an analogue of the human ErbB3 chain following Tyr 1257 (that is, Ala-Ala-Met-Gly-Ala-Cys-Pro-Ala-Ser-Glu-Gln-Gly), Tyr 1270 (that is, Glu-Glu-Met-Arg-Ala), Tyr 1241 (that is, Glu-Met-Asn-Arg-Gln), Tyr 1257 (that is, Ala-Ala-Met-Gly-Ala), Tyr 922 (that is, Met-Val-Met-Val-Lys), Tyr 1035 (that is, Met-Pro-Met-Asn-Gln), Tyr 1178 (that is, Glu-Tyr-Met-Asn-Arg), or Tyr 1203 (Glu-Tyr-Met-Asp-Val), (vii) in the case of p85 C-terminal SH2, especially the same sites as for p85 N-terminal SH2, (vii) in the case of PLC-γ C-terminal SH2, especially an analogue of the human PDGF receptor β chain following Tyr 1021 (that is, Ile-Ile-Pro-Leu-Pro), an analogue of the human PDGF receptor α chain following Tyr 1018 (that is, Ile-Ile-Pro-Leu-Pro), an analogue of the human ErbB2 chain following Tyr 1127 (that is, Val-Ala-Pro-Leu-Thr), (viii) in the case of PLC-γ N-terminal SH2 binding proteins, especially an analogue of the human basic FGF receptor I, II, II, IV chain following Tyr 766 (that is, Leu-Asp-Leu-X-X), an analogue of the human EGF receptor chain following Tyr 978 (that is, Leu-Val-Ile-Gln-Gly) or Tyr 1197 (that is, Leu-Arg-Val-Ala-Pro), an analogue of the human ErbB2 chain following Tyr 1248 (that is, Leu-Gly-Leu-Asp-Val), and (ix) in the case of SHPTP2 N-terminal SH2 binding proteins, especially an analogue of the human PDGF receptor β chain following Tyr 1009 (that is, Thr-Ala-Val-Gln-Pro) or Tyr 1021 (that is, Ile-Ile-Pro-Leu-Pro), an analogue of the human PDGF receptor α chain following Tyr 1018 (that is, Ile-Ile-Pro-Leu-Pro), Tyr 988 (that is, Ile-Gly-Val-Thr-Tyr) or Tyr 720 (that is, Val-Ile-Leu-Ser-Phe), an analogue of the human ErbB3 chain following Tyr 1159 (that is, Val-Met-Pro-Asp-Thr) or Tyr 471 (that is, Val-Ile-Val-Glu-Tyr), an analogue of the human Flt receptor type tyrosine kinase chain following Tyr 1169 (that is, Ile-Pro-Ile-Asn-Ala), an analogue of the human Kit receptor type tyrosine kinase chain following Tyr 568 (that is, Val-Tyr-Ile-Asp-Pro), an analogue of the human Ros receptor type tyrosine kinase chain following Tyr 234 (that is, Ile-Ile-Leu-Glu-Leu), an analogue of the human HGF receptor (Met) chain following Tyr 1367 (that is, Val-His-Val-Asn-Ala) or Tyr 1374 (that is, Val-Asn-Val-Leu-Cys);
and (x) most especially an analogue of the Epidermal Growth Factor Receptor (EGFR) sequence following Tyr 1068, the binding site for Grb2 SH2 (see Buday et al., Cell 73, 611-620 (1993)), that is the sequence Ile-Asn-Gln-Ser-Val-Pro-Lys-Arg-Pro-Ala-Gly-Ser-Val-Gln-Asn, preferably -Ile-Asn-Gln-Ser-, wherein in each case one or more amino acids are replaced by analogues which still allow for binding to the respective SH2-comprising protein, especially Grb2, or 1 or more amino acids are deleted, preferably 1 or more amino acids of the sequence -Ile-Asn-Gln-Ser-, more preferably 1, 2 or up to 3 amino acids of the sequence -Ile-Asn-Gln- being deleted. Preferably, the -Asn- in position 2 of the mentioned sequence following Tyr 1068 in EGFR is present as such, while the amino acids in the other positions may be replaced with one of the other amino acids mentioned above or (as far as the C-terminal amino acid(s) following the Asn are concerned) may be deleted.

More preferably, -(AA)$_n$- has one of the following meanings:

- A bivalent radical of a tetrapeptide of the formula -(AA$^1$)-(AA$^2$)-(AA$^3$)-(AA$^4$)- wherein -(AA$^1$)- is preferably selected from -lle-, -Cys(Acm)-, -Cys- (which preferably forms a disulfide bond with another -Cys- B), -AC$_3$C-, -AC$_6$C- and -Glu-.; -(AA$^2$)- is preferably selected from -Asn-, and also from -Glu- and -lle-, most preferably -Asn-; -(AA$^3$)- is preferably selected from -Gln-, -Cys(Acm)-, -Cys- (which preferably forms a disulfide bond with another -Cys- B); -lle- and -Pro-; and -(AA$^4$)- is preferably selected from -Cys(Acm)- and -Cys- (which preferably forms a disulfide bond with another -Cys- B);

- a bivalent radical of a tripeptide of the formula -(AA$^1$)-(AA$^2$)-(AA$^3$)- wherein -(AA$^1$)- is preferably selected from -lle-, -Cys(Acm)-, -Cys- (which preferably forms a disulfide bond with another -Cys- B) and -Glu-.; -(AA$^2$)- is preferably selected from -Asn-, and also from -Glu- and -lle-, most preferably -Asn-; and -(AA$^3$)- is preferably selected from -Gln-, -Cys(Acm)-, -Cys- (which preferably forms a disulfide bond with another -Cys- B); -lle- and -Pro-; or

- a bivalent radical of a dipeptide of the formula -(AA$^1$)-(AA$^2$)- wherein -(AA$^1$)- and -(AA$^2$)- preferably have the meanings given above, -(AA$^1$)- being especially -lle- and -(AA$^2$)- being especially -lle- or preferably -Asn-;

each of the mentioned amino acid radicals being present in the (D,L)- or preferably the D- or (most preferably ) the L-form.
A C-terminal protecting group Y is preferably an esterifying group, thus leading to an esterified C-terminal carboxy group. More preferred is a lower alkoxy group that is preferably branched in the 1-position of the lower alkoxy group or substituted in the 1- or 2-position of the lower alkoxy group by (one) suitable substituent(s).

A lower alkoxy group that is branched in the 1-position of the lower alkoxy group is, for example, tert-lower alkoxy, for example tert-butoxy.

A lower alkoxy group that is substituted in the 1- or 2-position of the lower alkoxy group by (one) suitable substituent(s) is, for example, arylmethoxy having one or two aryl radicals, wherein aryl is preferably phenyl that is unsubstituted or mono-, di-, or tri-substituted, for example, by lower alkyl, for example tert-lower alkyl, such as tert-butyl, lower alkoxy, for example methoxy, hydroxy, halogen, for example chlorine, and/or by nitro, for example benzyl oxy, benzyl oxy substituted by the mentioned substituents, for example 4-nitrobenzyl oxy or 4-methoxybenzyl oxy, diphenylmethoxy or diphenylmethoxy substituted by the mentioned substituents, for example di(4-methoxyphenyl)methoxy; 1-lower alkoxy-lower alkoxy, for example methoxy methoxy, 1-methoxyethoxy or 1-ethoxyethoxy, 1-lower alkyl-thio-lower alkoxy, for example 1-methylthiomethoxy or 1-ethylthioethoxy, aroyl methoxy wherein the aroyl group is preferably benzoyl that is unsubstituted or substituted, for example, by halogen, such as bromine, for example phenacyl oxy, 2-halo-lower alkoxy, for example 2,2,2-trichloroethoxy, 2-bromoethoxy or 2-iodoethoxy, as well as 2-(tri-substituted silyl)-lower alkoxy wherein the substituents are each independently of the others selected from lower alkyl, phenyl-lower alkyl, cycloalkyl or phenyl each of which is unsubstituted or substituted as above, for example 2-tri-lower alkyl siloxy-lower alkoxy, such as 2-tri-lower alkyl-silylethoxy, for example 2-trimethylsilylethoxy or 2-(di-n-butyl-methyl-silyl)-ethoxy, or tri-phenylsilylethoxy.

A C-terminal protecting Y group can furthermore be an organic silyloxy group.

An organic silyloxy group is, for example, a tri-lower alkyl silyloxy group, for example trimethylsilyloxy. The silicon atom of the silyloxy group can also be substituted by two lower alkyl groups, for example methyl groups.

A C-terminal protecting group Y is preferably tert-lower alkoxy, for example tert-butoxy, benzyloxy, 4-nitrobenzyl oxy, 9-fluorenlymethoxy or diphenylmethoxy.
A primary, secondary or tertiary amino group Y is preferably a free amino group, a mono- or disubstituted amino group the substituents of which are preferably selected from the group comprising lower alkyl, such as methyl, ethyl; isobutyl or 3-methylbutyl; octyl, such as 2-ethyl-hexyl; arylxy-lower alkyl, especially halonaphthyloxy-lower alkyl, such as 2-(1-bromonaphthalen-2-yloxy)-ethyl, or naphthyloxy-lower alkyl, such as 2-(naphthalen-2-yloxy or naphthalen-1-yloxy)-ethyl; aryl-lower alkyl, such as phenyl-lower alkyl, e.g. benzyl, 3-phenylpropyl, di-phenyl-lower alkyl, such as 2,2-diphenyl-ethyl or 3,3-diphenyl-propyl, (mono- or di- halo-phenyl)-lower alkyl, such as 2-(4-chlorophenyl)ethyl or 3-(2,4-dichlorophenyl)-propyl, naphthalene-lower alkyl, such as 3-naphthylpropyl or 3-naphthalen-2-ylpropyl, hydroxy-naphthalene-lower alkyl, such as 3-(2-hydroxy-naphthalen-1-yl)-propyl, or phenanthrenyl-lower alkyl, such as 3-phenanthren-9-yl-propyl; heterocyclyl-lower alkyl, such as pyrrolidinyl-lower alkyl, e.g. 2-(1-pyrrolidinyl)-ethyl, pyridyl-lower alkyl, e.g. 2-(2-pyridyl)-ethyl, furyl-lower alkyl, e.g. 2-furylmethyl, morpholinyl-lower alkyl, e.g. 2-(4-morpholinyl)-ethyl, and indolyl-lower alkyl, e.g. 2-(3-indolyl)-ethyl; cycloalkyl, such as cyclohexyl; and cycloalkyl-lower alkyl, such as cyclohexylmethyl. A disubstituted amino group may also be N-containing heterocyclyl bonded via its nitrogen atom, such as e.g. 1-pyrrolidinyl or 4-morpholino.

More preferably, a primary, secondary or tertiary amino group Y is a free amino group, a mono- or di-substituted amino group the substituents of which are preferably selected from the group comprising lower alkyl, e.g. methyl or ethyl, aryl-lower alkyl, such as phenyl-lower alkyl, e.g. benzyl, and heterocyclyl-lower alkyl, such as pyrrolidinyl-lower alkyl, e.g. 2-(1-pyrrolidinyl)-ethyl, pyridyl-lower alkyl, e.g. 2-(2-pyridyl)-ethyl, furyl-lower alkyl, e.g. 2-furylmethyl, morpholinyl-lower alkyl, e.g. 2-(4-morpholinyl)-ethyl, and indolyl-lower alkyl, e.g. 2-(3-indolyl)-ethyl. A disubstituted amino group may also be N-containing heterocyclyl bonded via its nitrogen atom, such as e.g. 1-pyrrolidinyl or 4-morpholino.

Preferably, Y is a primary, secondary or tertiary amino group as defined above, most preferably amino (-NH₂).

The proviso that two or more sulphydryl groups belonging to any amino acid A, B or AA are present as such or may form intramolecular disulfide bonds means that the respective peptide compounds of formula are present as cyclic compounds. It is to be interpreted so that, if an odd-numbered number of cysteine moieties is present, at least one sulphydryl
group per molecule is not part of a disulfide bond. Preferably, up to two cysteine moieties are present in a molecule of formula I; if two cysteine moieties are present, they may form an intramolecular disulfide bond, thus leading to pure constitution isomers.

Salts of compounds of formula I are especially acid addition salts, salts with bases or, where several salt-forming groups are present, can also be mixed salts or internal salts.

Salts are especially pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, from compounds of formula I having an acid group, for example a carboxy group, a sulfo group, or a phosphoryl group substituted by one or two hydroxy groups, and are, for example, salts thereof with suitable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIA and IIB of the Periodic Table of the Elements, especially suitable alkali metal salts, for example lithium, sodium or potassium salts, or alkaline earth metal salts, for example magnesium or calcium salts, also zinc salts or ammonium salts, as well as salts formed with organic amines, such as unsubstituted or hydroxy-substituted mono-, di- or tri-alkylamines, especially mono-, di- or tri-lower alkylamines, or with quaternary ammonium compounds, for example with N-methyl-N-ethylamine, diethylamine, triethylamine, mono-, bis- or tris-(2-hydroxy-lower alkyl)amines, such as mono-, bis- or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine or tris(hydroxy-methyl)aminoethylamine, N,N-di-lower alkyl-N-(hydroxy-lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, or N-methyl-D-glucamine, or quaternary ammonium salts, such as tetrabutylammonium salts. The compounds of formula I having a basic group, for example an amino group, can form acid addition salts, for example with inorganic acids, for example hydrohalic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with organic carboxylic, sulfonic, sulfo or phospho acids or N-substituted sulfamic acids, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, gluconic acid, glucaric acid, gluconic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid, as well as with amino acids, for example the α-amino acids mentioned hereinbefore, especially glutamic acid and aspartic acid, and with methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzene-sulfonic acid,
naphthalene-2-sulfonic acid, 2- or 3-phosphoglycerate, glucose-6-phosphate, N-cyclohexyl-sulfamic acid (forming cyclamates) or with other acidic organic compounds, such as ascorbic acid. Compounds of formula I having acid and basic groups can also form internal salts.

For isolation or purification purposes, it is also possible to use pharmaceutically unacceptable salts, for example a perchlorate or picolinate salt.

The compounds of the invention have useful, in particular pharmacologically useful, properties. Surprisingly, it has been found that the compounds of formula I are able to inhibit the interaction between SH2 domains of downstream regulatory proteins, such as Grb2, and phosphoproteins, especially phosphorylated protein tyrosine kinases, such as a phosphoprotein containing a -Tyr(PO$_4$)$_2$-X-Asn- motif, preferably phosphorylated EGFR protein tyrosine kinase (EGFR = Epidermal Growth Factor Receptor) or modified derivatives thereof, but in a broader sense also other phospho-proteins such as SHC or modified derivatives thereof, in a favourable way. They are thus useful in the treatment or prevention of diseases that respond to such inhibition.

The ability to inhibit the interaction between the SH2 domain of Grb2 and phosphorylated EGFR can be shown by the following type of assay: The principle of the assay is that a full-length or truncated phosphotyrosine protein immobilized on a solid phase is incubated with a chimeric SH2-GST (GST = glutathione S-transferase) protein or a full length SH2-containing protein-GST fusion protein capable of binding to it, in the presence of a test substance (for review, see Proc. Natl. Acad. Sci. USA 91, 83-87 (1994)). For example, the following procedure is used for the screening of inhibitors with regard to the interaction between Grb2 - for example, full-length (sequence: see Lowenstein et al., Cell 70, 431-42 (1992)) or SH2 alone - and phosphorylated EGFR (full-length cytoplasmic tyrosine kinase or a fusion product obtained from Maltose Binding Protein and the carboxy-terminal part of the EGF receptor ("tail" EGFR-MBP fusion protein)) (for EGFR sequence, see Nature 309, 418-425 (1984); for purified recombinant intracellular domain (ICD), see Eur. J. Biochem. 207, 265-75 (1992); the EGFR-MBP fusion protein is made as follows: Oligonucleotides flanking the entire carboxy-terminal half (nucleotides 3112 to 3816) of the EGFR and containing engineered EcoRI-HindIII restriction sites are used to amplify the appropriate DNA fragment by PCR. The amplified DNA fragment is recombined with purified EcoRI-HindIII-digested pMALc2 vector (New England Biolabs, Inc., Beverly, USA) downstream from and in the
same reading frame as the malE gene, which encodes maltose-binding protein (MBP). The vector containing the fused gene is transformed in E. Coli, and the fusion protein is expressed from the P_{lac} promoter. A crude cell extract is prepared and passed over a column of amylose resin. The fusion protein is then eluted with neutral buffer, containing maltose. Aliquots are frozen in liquid nitrogen and stored at -70 °C.

Wells of polystyrene microtiter plates (e.g. Nunc-Immuno Plate MaxiSorp™) are coated overnight at 4 °C in incubation buffer (20 mM Tris pH 7.5) with phosphorylated EGFR or "tail" EGFR-MBP fusion protein (phosphorylation conditions: 0.5 mg/ml of purified recombinant EGFR-ICD, or EGFR-MBP (+0.03mg/ml EGFR-ICD) is phosphorylated by the addition of 10 mM MnCl$_2$, 10 mM MgCl$_2$, 40 μM ATP in 20 mM Tris buffer pH 7.5 for 45 min). with a working solution containing 0.5 mg/ml of phosphorylated EGFR or MBP-EGFR. 11 ng/ml Grb2-SH2-GST (obtainable, e.g., from Santa Cruz Biotech, California, USA, or as follows: a cDNA clone encoding human Grb2 SH2 domain (e.g., aa 45-164) is amplified by polymerase chain reaction (PCR), using nucleotides with appropriate linkers, e.g. with BamH1 (5'),3' EcoRI linkers; the purified (e.g. BamH1-EcoRI) fragments from PCR products are then subcloned in-frame into the appropriate (e.g. BamH1-EcoRI) restriction sites of an appropriate vector (e.g. pGEX-3X, Pharmacia, Uppsala, Sweden) - comparable results are also obtained when using full length Grb2, see also Embo J. 13, 4011-21 (1994)] are then added to coated phosphorylated EGFR or "tail" EGFR-MBP fusion protein for 2 h at room temperature in the absence or presence of test substance of formula I dissolved in buffer = dimethyl sulfoxide (maximally 25%). Bound SH2 is detected with polyclonal rabbit anti-GST antibody (obtained by immunisation of rabbits with glutathione-S-transferase) for 1 h at room temperature. Bound antibody is then detected after the addition of peroxidase-conjugated goat-antirabbit IgG (EIA Grade Affinity purified Goat Anti-Rabbit IgG (H+L) - Horseradish Peroxidase Conjugate from Bio-Rad, Hercules, USA) and incubation for 1 h at room temperature. Peroxidase activity is then monitored at 655 nm on a plate reader by the addition of a TMB substrate (Single Component TMB Peroxidase EIA Substrate Kit from Bio-Rad, Hercules, USA; TMB = 3,3',5,5'-tetramethylbenzidine solution).

With this type of assay, IC$_{50}$ values (= the concentrations where half-maximal inhibition of the interaction is found) in the range of 10$^{-5}$ to 10$^{-10}$, more preferably in the range of 10$^{-6}$ to 10$^{-10}$ M) are found with test compounds of formula I.
This type of assays is not limited to the EGF receptor - it can also be used analogously with erb-B2 or other protein tyrosine kinases. Furthermore, it is possible to use other SH2 domains instead of Grb2 SH2. For example, the interactions of the SH2-comprising proteins and phosphotyrosine comprising proteins mentioned above in the definition of a bivalent radical -(AA)ₘ⁻ in formula I as an analogue of an SH2 domain binding site of a protein with phosphotyrosine of a mammal can be tested.

In addition, it can be shown by methods known in the art that injection of a compound of formula I into mammalian cells leads to a stop of cell growth (the test can be made in analogy to the well-known method of microinjection of antibodies into mammalian cells in which it has been shown that microinjection of antibodies against Grb2 blocks the induction of S phase entry in response to EGF and PDGF, see EMBO J. 12, 3467-73 (1993); or to the well-known methods for cell permeabilization where a) a phosphorylated peptide encompassing Tyr 716 (an autophosphorylation site) in the PDGFR kinase insert has been shown to significantly inhibit the activation of Ras by PDGF in permeabilized PAE cells as well as fibroblasts (see Mol. and Cell. Biol., 6715-26 (1994)), or b) the effect of various phosphopeptides on the activation of guanine nucleotide exchange on Ras by EGF and NGF has been studied in permeabilised 6-24 cells, the EGFR-Tyr 1068 phosphopeptide corresponding to an autophosphorylation site for Grb2 on the EGFR showing inhibition of EGF and NGF stimulation of Ras by 96% and 98%, respectively, at 50 µM concentration (Oncogene 9(12), 3483-3491 (1994)).

The compounds of the invention, due to their ability to uncouple a phosphorylated protein, especially a protein tyrosine kinase, e.g. EGF receptor, from a respective SH2 containing protein, e.g. the SH2-containing Grb2, are able to inhibit subsequent cellular signal transduction pathways important for diseases such as viral, inflammatory, allergic, auto-immune, cardiovascular and especially proliferative diseases, such as for malignant hyperproliferative diseases, e.g. tumor diseases, preferably breast cancer, chronic myelogenous leukemia (CML), thyroid carcinoma and osteosarcoma, or for hyperproliferation of epithelial cells, e.g. psoriasis, are appropriate for the treatment and prophylaxis of said diseases.

Therefore, the compounds of the present invention are useful for the treatment of diseases that respond to inhibition of the interaction of (a) protein(s) comprising (an) SH2 domain(s)
and a phosphoprotein, preferably a protein tyrosine kinase or a modified version thereof, more preferably of Grb2 SH2 with EGFR or modified derivatives thereof. The term "modified version" or "modified derivative" means mainly a derivative that is causative or active in the establishment of diseases, e.g. truncated versions, virus derived analogues, etc.

The treatment can also, e.g. in the case of hematopoietic cell proliferative disorders, such as leukemias, be used in conjunction with autologous bone marrow transplantation and chemotherapy techniques. For example, an aliquot of bone marrow cells (even one cell or some single cells, which may be treated by microinjection of a compound of the invention as described above) are obtained from a patient, e.g. from the pelvis. The cells are then cultured in the presence of a compound of formula I (which may also be applied by microinjection) which is able to disrupt the protein tyrosine kinase/SH2-comprising protein interaction. Thus blocking the signal transduction pathway of those bone marrow cells capable of forming complexes resulting from such interaction, it is possible to select against the presence of clonal daughter cells derived from these cells and to purge the culture(s) of these cells from those responsible for the hematopoietic cell proliferative disorder being treated. After chemotherapeutic and/or radiotherapeutic treatment of the patient from whom the cells have been obtained, the patient can receive an autologous infusion of cultured bone marrow cells resulting from the above purging procedure.

Due to their high binding affinity to SH2 domains, such as those of Grb2, the compounds of formula I can also be bound covalently to chromatographic materials, thus making it possible to produce chromatographic materials for the affinity purification of natural or recombinant SH2-domains or SH2-comprising proteins from the cells of living organisms. For example, a compound of formula I with an appropriate free functional group (e.g. -NH₂, -SH, -OH and/or -COOH) can be attached covalently to activated or activatable matrices appropriate for chromatography, e.g. cyanogen bromide activated matrices, epoxy-activated matrices, nitrophenyl chloroformate and N-hydroxysuccinimide chloroformate. polyacrylthiazido agarose, oxirane acrylic beads, bromoacyetl-cellulose, epichlorhydrin-activated matrices, tresyl-chlordie-activated agarose, vinylsulfone-activated agarose, and the like. Preferred activated or activatable coupling gels for affinity chromatography include but are not limited to

a) for coupling of compounds of formula I with an -NH₂ group employed for binding: cyanogen bromide activated Sepharose 4B; ECH Sepharose 4B (carbodiimide coupling
method used most often in analogy to process for preparation of compounds of formula I as described below; or activated CH Sepharose 4B;
b) for coupling of compounds of formula I with an -NH₂ and/or an -SH group: Tresyl-activated Sepharose 4B;
c) for coupling of compounds of formula I with an -NH₂,-OH and/or -SH group: epoxy-activated Sepharose 6B; and
d) for coupling of compounds of formula I with a -COOH group: EAH Sepharose 4B (carbodiimide method for coupling most often used in analogy to process for preparation of compounds of formula I as described below).

Sepharose stands for agarose derived chromatographic materials and is a trademark from Pharmacia, Uppsala, Sweden, from where the mentioned gels are available.

In the following definitions of preferred compounds, general terms may be replaced by their more specific (more preferred) definitions as given above in order to obtain more preferred compounds.

Preferred is a compound of formula I wherein

m is 2 to 6, more preferably 2, 3 or 4;

X is selected from

(i) benzoyl, 1-naphthoyl, 2-naphthoyl and, even more preferably, from benzoyl substituted with amino; lower alkylamino; amino-lower alkyl; hydroxy; lower alkoxy; amino and hydroxy; amino and lower alkoxy; carboxy; lower-alkoxycarbonyl; cyano; halogen, especially chloro; lower-alkythio; or lower alkylsulfenyl, and from 1- or 2-naphthoyl substituted with amino; especially from 4-aminobenzoyl, 3-aminobenzoyl (more preferred), 2-aminobenzoyl (most preferred); 3,5-diaminobenzoyl; 4-lower alkylamino-benzoyl, such as 4-methylamino-benzoyl, 4-aminobenzoyl, 4-(amino-lower alkyl)-benzoyl, such as 4-(methylamino)-benzoyl, 4-hydroxybenzoyl, 2-hydroxybenzoyl, 4-lower alkylxy-, such as 4-methoxybenzoyl, 4-amino-2-hydroxybenzoyl, 4-amino-3-lower alkoy-benzoyl, such as 4-amino-3-methoxy-benzoyl, 4-carboxybenzoyl, 4-lower alkoxycarbonyl-benzoyl, such as 4-methoxycarbonyl-benzoyl, 4-cyanobenzoyl, 4-lower alkylthio-benzoyl, such as 4-methylthiobenzoyl, 4-lower alkylsulfenyl-benzoyl, such as 4-lower methylsulfenyl-benzoyl and aminonaphthoyl, such as 3-amino-2-naphthoyl; and most preferably from 4-aminobenzoyl, 3-aminobenzoyl (more preferred), 2-
aminobenzoyl (most preferred); 3,5-diaminobenzoyl; 2-hydroxybenzoyl, 4-lower alkoxy-, such as 4-methoxybenzoyl, and 3-amino-2-naphthoyl;

(ii) 1-or 2-naphthalenesulfonyl which is substituted with amino or mono- or di-lower alkylamino, such as dimethylamino; especially 5-dimethylamino-naphthalene-1-sulfonyl;

(iii) C₃-C₇-cycloalkylcarbonyl, such as cyclohexylcarbonyl, which is unsubstituted or substituted by amino; most preferably 1-amino-cyclohexylcarbonyl or 1-amino-cyclopentylcarbonyl;

(iv) pyridylcarbonyl which is unsubstituted or substituted with amino, such as pyridin-4-yl- or pyridin-3-ylcarbonyl, or amino-pyridin-3-yl-carbonyl, such as 2- or 6-amino-pyridin-3-ylcarbonyl; pyrazinyl, such as pyrazin-2-yl, which is unsubstituted or substituted with amino, such as in 3-amino-pyrazin-2-ylcarbonyl, quinolinyl-carbonyl, such as quinoline-2-, quinoline-3-, quinoline-4- or quinoline-8-ylcarbonyl, isoquinolyl, such as isoquinoline-1-yl, indolylcarbonyl, such as indole-5-yl-, indolyl-3-yl- or indole-2-yl-carbonyl; and indolylcarbonyl, such as indolin-2-yl-carbonyl, the latter being especially preferred; and

(v) quinolinylsulfonyl, such as quinoline-8-ylsulfonyl;

A is absent or the bivalent radical of a natural or unnatural amino acid, preferably selected from glycine, alanine, β-alanine, valine, norvaline, leucine, isoleucine, norleucine, α-amino-n-decanoic acid, serine, homoserine, threonine, methionine, cysteine, which can form a disulfide bridge with another cysteine B or AA; S-protected cysteine, such as S-acetylaminomethyl-cysteine, proline, trans-3- and trans-4-hydroxyproline, phenylalanine, tyrosine, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenylserine, phenylglycine, α-naphthylalanine, cyclohexylalanine, cyclohexylglycine, tryptophan, indole-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aspartic acid, asparagine, aminomalonic acid, aminomalonic acid monoamide, glutamic acid, glutamine, histidine, arginine, lysine, N'-benzyl-N'-methyl-lysine, N',N'-dibenzylylysine, δ-hydroxyllysine, ornithine, α,γ-diaminobutyric acid and α,β-diaminopropionic acid; it being possible for each of the mentioned amino acids (with the exception of glycine or any other amino acid without asymmetric carbon atom) to be in the D-, L- or (D,L)-form,
preferably in the L- or in the D-form; most preferably A is absent or the bivalent radical of proline which is present in the (D,L)-, D- or preferably L-form;

B is the bivalent radical of a natural or unnatural amino acid as defined above for A, preferably being selected from proline or especially S-acetamidomethyl-cysteine, cysteine which may form a disulfide bond with another cysteine A or AA, glutamic acid, aspartic acid, glycine, alanine, valine, leucine, isoleucine and β-alanine, it being possible for each of the mentioned amino acids (with the exception of glycine or any other amino acid without asymmetric carbon atom) to be in the D-, L- or (D,L)-form, preferably in the L- or in the D-form; most preferably, B is selected from glutamic acid, S-acetamidomethyl-cysteine, cysteine which together with another cysteine AA forms a disulfide bond; glycine, alanine and isoleucine which being possible for each of the mentioned amino acids (with the exception of glycine or any other amino acid without asymmetric carbon atom) to be in the D-, L- or (D,L)-form, preferably in the L- or in the D-form;

PTI is a bivalent radical of phosphotyrosine (in the D-, L- or less preferably the (D,L)-form) or of a phosphotyrosine mimic in the form of a bivalent radical (which is bound N-termally via the imino group resulting from the α-amino group and C-termally via the carbonyl group resulting from its α-carboxy group) of an amino acid selected from phosphonomethyl-phenylalanine, especially 4-phosphono-methyl-phenylalanine, phosphono-(α-fluoro)methyl-phenylalanine, especially 4-phosphono-(α-fluoro)methyl-phenylalanine, phosphono-(α,α-difluoro)methyl-phenylalanine, especially 4-phosphono-(α,α-difluoro)methyl-phenylalanine, phosphono-(α-hydroxy)methyl-phenylalanine, especially 4-phosphono-(α-hydroxy)methyl-phenylalanine, O-sulfo-tyrosine, such as 4-(O-sulfo)tyrosine, dicarboxymethoxy-phenylalanine (= HOOC)₂-CH₂-O-phenylalanine, especially 4-(dicarboxymethoxy)-phenylalanine aspartic acid, glutamic acid, phosphoserine and phosphothreonine, each of which is present in the (D,L)-, D- or preferably the L-form;

-(AA)ₙ- has one of the following meanings:

• a bivalent radical of a tetrapeptide of the formula -(AA¹)-(AA²)-(AA³)-(AA⁴)- wherein
  -(AA¹)- is preferably selected from -Ile-, -Cys(Acm)-, -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B), -Ac₅c-, -Ac₆c- and -Glu-; -(AA²)- is preferably selected from -Asn-, and also from -Glu- and -Ile-, most preferably -Asn-;
(AA³)- is preferably selected from -Gln-, -Cys(Acm)-, -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B); -Ile- and -Pro-; and -(AA³)- is preferably selected from -Cys(Acm)- and -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B);

- a bivalent radical of a tripeptide of the formula -(AA¹)- (AA³)-(AA³)- wherein -(AA¹)- is preferably selected from -Ile-, -Cys(Acm)-, -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B) and -Glu-; -(AA³)- is preferably selected from -Asn-, and also from -Glu- and -Ile-, most preferably -Asn-; and -(AA³)- is preferably selected from -Gln-, -Cys(Acm)-, -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B); -Ile- and -Pro-; or

- a bivalent radical of a dipeptide of the formula -(AA¹)-(AA³)- wherein -(AA¹)- and -(AA³)- preferably have the meanings given in the last paragraph, -(AA¹)- being especially -Ile- and -(AA³)- being especially -Ile- or preferably -Asn-;

each of the mentioned amino acid radicals being present in the (D,L)- or preferably the D- or (most preferably ) the L-form;

and

Y is a free amino group (preferred), a mono- or disubstituted amino group the substituents of which are preferably selected from the group comprising lower alkyl, e.g. methyl or ethyl, phenyl-lower alkyl, e.g. benzyl, pyrrolidinyl-lower alkyl, e.g. 2-(1-pyrrolidinyl)-ethyl, pyridyl-lower alkyl, e.g. 2-(2-pyridyl)-ethyl, furyl-lower alkyl, e.g. 2-furylmethyl, morpholinyl-lower alkyl, e.g. 2-(4-morpholinyl)-ethyl, and indolyl-lower alkyl, e.g. 2-(3-indolyl)-ethyl; or is 1-pyrrolidinyl or 4-morpholinyl,

with the proviso that two or more sulfhydryl groups belonging to any amino acid A, B or AA are present as such or may form intramolecular disulfide bonds,

or a salt thereof.

More preferred is a compound of formula I wherein

m is 2, 3 or 4,
X is selected from 4-aminobenzoyl, 3-aminobenzoyl (more preferred), 2-aminobenzoyl (most preferred); 3,5-diaminobenzoyl; 2-hydroxybenzoyl, 4-lower alkoxy-, such as 4-methoxybenzoyl, and 3-amino-2-naphthoyl;

A is absent or the bivalent amino acid radical of proline which is present in the (D,L)-, D- or preferably L-form; preferably, A is absent;

B is selected from glutamic acid, S-acetamidomethyl-cysteine, cysteine which together with another cysteine AA forms a disulfide bond; glycine, alanine and isoleucine, it being possible for each of the mentioned amino acids (with the exception of glycine or any other amino acid without asymmetric carbon atom) to be in the D-, L- or (D,L)-form, preferably in the L- or in the D-form;

PTI is a bivalent radical of phosphotyrosine (in the D-, L- (most preferred) or (less preferably) the (D,L)-form) or of a phosphotyrosine mimic of the phosphono-(α,α-difluoro)methyl-phenylalanine type, especially 4-phosphono-(α,α-difluoro)methyl-phenylalanine

-(AA)ₙ- has one of the following meanings:

- a bivalent radical of a tetrapeptide of the formula -(AA¹)-(AA²)-(AA³)-(AA⁴)- wherein -(AA¹)- is selected from -Ile-, -Cys(Acm)-, -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B) and -Glu-; -(AA²)- is selected from -Asn-, and also from -Glu- and -Ile-, most preferably -Asn-; -(AA³)- is selected from -Gln-, -Cys(Acm)-, and -Cys-; and -(AA⁴)- is selected from -Cys(Acm)- and -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B);

- a bivalent radical of a tripeptide of the formula -(AA¹)-(AA²)-(AA³)- wherein -(AA¹)- is selected from -Ile-, -Cys(Acm)-, -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B) and -Glu-; -(AA²)- is selected from -Asn- and -Ile-, most preferably -Asn-; and -(AA³)- is selected from -Gln-, -Cys(Acm)- and -Cys- (which is present as such or preferably forms a disulfide bond with another -Cys- B); or

- a bivalent radical of a dipeptide of the formula -(AA¹)-(AA²)- wherein -(AA¹)- is -Ile- and -(AA²)- is -Ile- or preferably -Asn-;
each of the mentioned amino acid radicals being present in the the L-form or, in the case of
-Cys- or -Cys(Acm)-, in the D- or L-form;

and

Y is amino (-NH₂),

with the proviso that two or more sulfhydryl groups belonging to any amino acid B or AA are
present as such or may form intramolecular disulfide bonds,

or a salt thereof.

Especially preferred is a compound mentioned in the examples, or a (preferably
pharmaceutically acceptable) salt thereof.

Most preferred is a compound of formula I being selected from the following compounds:

2-Aminobenzoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 1);

2-aminobenzoyl-Cys(Acm)-Tyr(PO₃H₂)-Ile-Asn-Cys(Acm)-NH₂
(SEQ ID NO: 5);

2-aminobenzoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-NH₂
(SEQ ID NO: 6);

2-aminobenzoyl-Ala-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 18);

2-aminobenzoyl-Gly-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 20)

3-aminobenzoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 23);

2-aminobenzoyl-Ile-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 29);

indoline-2-ylcarbonyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 31);

3-aminobenzoyl-Glu-F₂Pmp-Ile-Asn-Glu-NH₂
(SEQ ID NO: 36);
2-aminobenzoyl-Cys-Tyr(PO$_3$H$_2$)-Ile-Asn-Gin-Cys-NH$_2$

| S---------------------S

(SEQ ID NO: 38);

2-Aminobenzoyl-Glu-Tyr(PO$_3$H$_2$)-Ac$_{6c}$-Asn-NH$_2$
(SEQ ID NO: 42);

2-Aminobenzoyl-Glu-Tyr(PO$_3$H$_2$)-Ac$_{6c}$-Asn-NH$_2$
(SEQ ID NO: 43); and

2-Aminobenzoyl-Phe-Tyr(PO$_3$H$_2$)-Ile-Asn-NH$_2$
(SEQ ID NO: 44);

or a pharmaceutically acceptable salt thereof if a salt-forming group is present.

The compounds of the present invention can be synthesized according to known procedures, especially by a process comprising reacting a fragment of a compound of formula I, which has a free carboxy group or a reactive derivative thereof, or, in the case of the introduction of X, a free carboxy or sulfo group, or a reactive derivative thereof, with a complementary fragment that has an amino group with at least one free hydrogen atom, or with a reactive derivative thereof, with formation of an amide bond; in the mentioned fragments free functional groups with the exception of those that participate in the reaction if required being present in protected form; and removing any protecting groups present;

and, if desired, transforming a compound of formula I into a different compound of formula I; transforming a salt of an obtainable compound of formula I into the free compound or a different salt or an obtainable free compound of formula I into a salt; and/or separating obtainable mixtures of isomers of compounds of formula I into the individual isomers.

In the following, more detailed description of the preferred process conditions, X, A, B, PTI, -(AA)$_m$-, m and Y have the meanings given for compounds of the formula I, if not mentioned otherwise.

**Detailed description of preferred reaction conditions**
The compounds of the present invention preferably can be readily prepared according to well-established, standard liquid or, preferably, solid-phase peptide synthesis methods, general descriptions of which are broadly available (see, for example, in J.M. Stewart and J.D. Young, Solid Phase Peptide Synthesis, 2nd edition, Pierce Chemical Company, Rockford, Illinois (1984), in M. Bodansky and A. Bodansky, The Practice of Peptide Synthesis, Springer Verlag, New York (1984); and Applied Biosystems 430A Users Manual, ABI Inc., Foster City, California), or they may be prepared in solution, by the liquid phase method or by any combination of solid-phase, liquid phase and solution chemistry, e.g. by first completing the respective peptide portion and then, if desired and appropriate, after removal of any protecting groups being present, by introduction of the residue X by reaction of the respective carbonic or sulfonic acid or a reactive derivative thereof.

A fragment with a free carboxy or sulfonic group can be an amino acid (if required, in suitably protected form) or a di- or other appropriate oligopeptide or also (in the case of the introduction of the N-terminal X of compounds of formula I with acylated or sulfonylated terminal amino group) the acylating carbonic or sulfonic acid. A fragment that has an amino group with at least one free hydrogen atom (= a group -NH-) can also be a single amino acid, a di- or other oligopeptide or, in the case of preparation of peptamides (Y = amino or mono- or disubstituted amino), ammonia or mono- or disubstituted ammonia.

Reactive derivatives of carbonic or sulfonic acids are preferably reactive esters, reactive anhydrides or reactive cyclic amides. Reactive carbonic acid or reactive sulfonic acid derivatives can also be formed in situ.

A reactive derivative of an "amino group with at least one free hydrogen" is preferably derivatized by the reaction with a phosphite, such as diethyl-chlorophosphite, 1,2-phenylene-chlorophosphite, ethyl-dichlorophosphite, ethylene-chlorophosphite or tetraethylpyrophosphite; or is present in the form of a carbamic acid chloride wherein the amino group participating in the reaction is substituted by halocarbonyl, such as chlorocarbonyl. Preferably, free amino is used instead of a reactive derivative.

The reaction steps required e.g. for the synthesis of amide or sulfonamide bonds usually depend on the type of activation of the carboxylic or sulfo group participating in the reaction. The reactions normally run in the presence of a condensing agent or, when activating the
carboxylic or sulfonic acids in the form of anhydrides, of an agent that binds the carboxylic or sulfonic acid formed. In some cases it is also possible to add chaotropic agents such as LiF in N-methylpyrrolidin-2-one. The reactions are especially carried out in a temperature range from -30 to +150 °C, preferably from +10 to +70 °C, and, most preferably, from +20 to +50 °C, if appropriate, in an inert gas atmosphere, e.g. under nitrogen or argon.

If desired or appropriate, unreacted amino groups can be acylated after a reaction cycle, e.g. by acetylation of unreacted amino groups with an excess of acetic anhydride/pyridine/DMA (1:1:8), thus facilitating later purification of the final product.

In general, a suitably protected amino acid as a ligand is attached via its carboxyl group (-COOH) to a derivatized, insoluble polymeric support, e.g. a cross-linked polystyrene or polyamide resin, such as a 4-(2',4'-dimethoxyphenyl-[hydroxy- or amino-]methyl)-phenyloxypolystyrene resin (the polymer is, e.g., a copolymer of styrene with 1% divinylbenzene, 100-200 mesh) or a PAL-PEG-PS (synonym: PAL-PEG-MBHA-PS) resin (PAL stands for a trisalkoxy, especially trismethoxy, benzylamide linker; PEG for polyethylene glycol; and MBHA for 4-methylbenzyldiamine - in this type of resin, polystyrene (PS) supports uniformly incorporate a derivatized polyethylene glycol (PEG) spacer between the functional group on the PS gel bead (e.g. preferred particle size in the range of 75 to 150 μm, crosslinking by 1% divinylbenzene) and the handle or attachment point of the peptide to be synthesized (see J. Org. Chem. 55, 3730 (1990) or in "Peptides: Chemistry and Biology, Proceedings of the Twelfth American Peptide Symposium (Smith, J.A., and Rivier, J.E., eds.) Escom, Leiden, The Netherlands (1992), p. 603)) by condensation reactions. "Suitably protected" refers to the presence of protecting groups on the amino group (e.g. α-NH₂ or β-NH₂) and any side-chain functional group (if present) of the amino acid. Di-, tri- or other oligopeptides can be used instead of the amino acids as building blocks (fragments).

Synthesis proceeds in a stepwise, cyclical fashion by successively removing the NH₂ protecting group of the amino group to be reacted next and then coupling an activated fragment (e.g. an amino acid, di-, tri- or oligopeptide or the carboxylic acid or sulfonic acid of formula II,

\[
\text{X-OH} \quad \text{(II)}
\]
or a reactive derivative thereof, wherein X has the meanings given under formula I) to the deprotected NH₂ (e.g. α- or β-NH₂). Preferably, activation of the COOH group of the amino acid to be reacted or ( in the case of the introduction of X) the carboxyl or sulfo group of the acid of of formula II to be attached by the condensation reaction is effected

(i) directly with a carbodiimide, e.g. dicyclohexylcarbodiimide (DCC), N-ethyl-N’-(3-dimethylaminopropyl)-carbodiimide, N,N’-diethylcarbodiimide or N,N’-diisopropylcarbodiimide (DICD); with a carbonyl compound such as carbonyldimidazole; with 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3’-sulfonate and 2-tert-butyl-5-methylisoxazolium perchlorate; with acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline; with N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU) ; with an uronium compound such as 2-((1H-benzo[d]azol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (HBTU) or 2-((pyridin-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate = O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate (TPTU); or phosphonium compounds such as benzotriazol-1-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) or benzotriazol-1-yl-oxy-pyrrolidino-phosphonium hexafluorophosphate (PyBOP);

(ii) via formation of the symmetric anhydride (obtainable, for example, by condensation of the corresponding acid in the presence of a carbodiimide or 1-diethylaminopropyn; symmetric anhydrides method), or an asymmetric anhydride, such as the respective carbonic or sulfonic acid bromide, chloride or fluoride (obtainable, for example, by treatment of the respective carbonic or sulfonic acid with thionyl-, phosphopenta- or oxaly-fluoride, -chloride or -bromide; acid halide (e.g. chloride) method), or

(iii) by formation of an "active ester", e.g. an amino- or amido ester, such as a N-hydroxybenzotriazole (HOBT) or N-hydroxysuccinimide ester, or an aryl ester, such as a pentafluorophenyl, 4-nitrophenyl or 2,4,5-trichlorophenyl ester (obtainable by treatment of the respective acid with a phenyl with the appropriate substituents, such as 4-nitrophenol or 2,4,5-trichlorophenol, and the like);

or by an appropriate combination of any of the reagents and reactions mentioned under (i) to (iii).
Useful acid binding agents that can be employed in the condensation reactions are, for example, alkaline metals, carbonates or bicarbonates, such as sodium or potassium carbonate or bicarbonate (if appropriate, together with a sulfate), or organic bases such as sterically hindered organic nitrogen bases, for example tri-lower alkylamines, such as N,N-diisopropyl-N-ethylamine, pyridine or N-methyl-pyrrolidin-2-one, which can be used alone or in any appropriate combination.


Examples for hydroxy protecting groups are acyl radicals, such as tert-lower alkoxy carbonyl radicals, for example tert-butoxycarbonyl, etherifying groups, such as tert-lower alkyl groups, for example t-butyl, or silyl- or tin radicals, such as tert-butyl-dimethylsilyl or the tri-n-butyltin radical.

Carboxy groups can be protected by groups as defined above for the C-terminal protecting groups Y, preferably by esterifying groups selected from those of the tert-butyl type, from benzyl, from trimethylsilyl-ethyl and from 2-triphenylsilyl groups, or they can be protected as lower alkenyl esters, such as allylic esters.

Amino or guanidino (e.g. in H-Arg-OH) groups can be protected by removable acyl groups or by arylmethyl, etherified mercapto, 2-acyl-lower alk-1-enyl, a silyl group or an organic
sulfonyl group or tin amino protecting groups; tert-butoxycarbonyl, allyloxycarbonyl, benzyl-
oxycarbonyl, 4-nitrobenzylloxycarbonyl, 2-chlorobenzylloxycarbonyl, 2-bromobenzyloxy-
carbonyl, diphenylmethoxycarbonyl, nitrophenylsulfenyl, 2,2,2-trichloroethoxy carbonyl,
2,2,5,7,8-pentamethylchroman-6-sulfonyl (PMC - very preferred), 2,2,4,6,7-pentamethyl-
dihydrobenzofuran-5-sulfonyl (Pbf) or 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr) being
especially preferred.

Carbamide groups (for example, in the side chains of asparagine and glutamine) can be
protected at the nitrogen atom by arylmethyl groups, preferably triphenylmethyl (trityl) or
analogues thereof with one or more lower alkoxy, such as methoxy, and/or lower alkyl, such
as methyl, substituents in one or more phenyl rings.

Imino groups (e.g. in imidazole) can be protected by 2,4-dinitropheryl, trityl, tert-butoxy-
carbonyl or p-toluenesulfonyl, or (e.g. in indole) by formyl or tert-butoxycarbonyl.

Mercapto groups can be protected, e.g., by acetamidomethyl, by trityl or by p-methylbenzyl.

Phospho groups can be protected in the form of their diesters, especially in the form of their
di-lower alkyl esters, such as the di-methyl ester, the di-ethyl ester or the di-tert-butylester.

A large number of methods of removing protective groups in the final products or any inter-
mediates are known in the art and comprise, inter alia, β-elimination, solvolysis, hydrolysis,
alcoholysis, acidolysis, photolysis, enzymatical removal, treatment with a base or reduction.

The protective groups are usually removed after the complete synthesis of the resin-bound
molecule by conventional methods of peptide chemistry, conveniently by treatment with
95 % trifluoroacetic acid (Fmoc-chemistry). In some cases, strong nucleophiles, such as
dimethylsulfide and/or 2-ethanedi ethanol, may be additionally added to capture the generated
compounds resulting from the protecting groups, e.g. in a combination such as trimethyl-
silyl trifluoro-methansulfonate/dimethylsulfide/trifluoroacetic acid/ethanedi thiol/m-cresol.

The two preferred methods of solid phase peptide synthesis are the Boc and the Fmoc
methods, which are named with reference to their use of the tert-butoxycarbonyl (Boc) or 9-

In the more established Boc method, the acid-lability of the Boc group is exploited and trifluoroacetic acid (TFA) treatment is used in order to remove the protective group. Preferred third groups as protecting groups (for functional groups in side chains) are relatively stable in weak acid, e.g. TFA. Most can be cleaved by strong acids such as hydrofluoric acid (HF) or trifluoromethanesulfonic acid. A small number of side chain groups (e.g. 2,4-dinitrophenyl protected imino in the histidyl side chain) may require a separate deprotection step, e.g. treatment with thiophenol or ammonolysis. After synthesis, the product is typically cleaved from the resin and simultaneously deprotected by HF treatment at low temperature (e.g. around 0 °C).

The Fmoc-group can be cleaved off preferably in the presence of a mild nitrogen base, preferably piperidine, in an inert solvent, preferably dimethyl acetamide, thereby allowing the use of side-chain protecting groups which are labile to milder treatment, e.g. TFA.

Preferably, an acid labile ether resin such as HMP-resin (p-hydroxymethylphenoxymethyl polystyrene), 4-(2',4'-dimethoxyphenyl-hydroxymethyl)-phenoxy-polystyrene (Rink-resin), or a resin with a benzyloxy- or alkylloxy linker (see Wang, J. Amer. Chem. Soc. 95, 1328 (1973); or, for the synthesis of compounds with a C-terminal amino group Y (forming a carbamamide) which are preferred, 4-(2',4'-dimethoxyphenyl-aminomethyl)-phenoxy-polystyrene or -phenoxyethyl-polystyrene (Rink et al., Tetrahedron. Lett. 28(33), 3787-90 (1987); Novabiochem, Läufelfingen, Switzerland); or a PAL-PEG-PS resin (Millipore, Bedford, USA) is used as the solid support, permitting simultaneous cleavage/deprotection in TFA.

Additional process steps
Compounds of formula I can be transformed into different compounds of formula I, e.g. by oxidation, hydrolysis and the formation of disulfide bonds.

For the preferred oxidation of mercapto groups, e.g. lower alkyl-mercapto groups, such as methyithio, which are preferably oxidised to the respective sulfinyl groups, e.g. lower alkyl sulfinyl, such as methylsulfinyl, organic or preferably inorganic peroxides, such as hydrogen peroxide, can be employed. For example, reaction of lower alkylthio compounds with hydrogen peroxide in concentrations from 2 to 30 volume-% at preferred temperatures from 0 to 50 °C, especially around room temperature, leads to the respective lower alkyl sulfinyl compounds.

For the preferred hydrolysis of esterified carboxy groups, such as lower alkoxy carbonyl groups, well-known conditions for hydrolysis are used, for example hydrolysis in the presence of a base, e.g. a hydroxide of an alkaline metal, such as sodium hydroxide, under conditions known in the art, e.g. in an aqueous solvent at preferred temperatures between 0 and 50 °C, preferably at room temperature.

For the preferred formation of disulfide bridges (preferably intramolecular), it is possible to start from the respective free or preferably the respective S-protected compounds, either first removing the mercapto protecting group by methods known in the art, or more preferably (in the case where in the compounds of formula I the mercapto groups to be reacted are present in the acetamidomethyl protected form) by simultaneous deprotection and oxidation, e.g. in the presence of iodine, preferably in an excess, e.g. the 2- to 10-fold molar amount compared to the compound of formula I, in an aqueous-organic solvent mixture, such as acetic acid in water, at preferred temperatures in the range from 0 to 50 °C, more preferably around room temperature.

Salts of compounds of formula I having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of formula I having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g. the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or
with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of formula I are obtained in customary manner, e.g. by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of formula I containing acid and basic salt-forming groups, e.g. a free carboxy group and a free amino group, may be formed, e.g. by the neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g. with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by e.g. medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Starting materials:

The present invention relates also to novel starting materials and/or intermediates and to processes for their preparation. The starting materials used and the reaction conditions selected are preferably those that result in the compounds described as being preferred.

Unless a specific method of synthesis is indicated for starting materials, the starting materials are known, can be prepared according to processes known per se, especially in analogy to methods given in the Examples, and/or are commercially available.

For example, suitably protected and/or preactivated D-, (D,L)- or L- amino acids, unnatural amino acids, di-, tri- or oligopeptides, derivatized and/or preloaded resins, the ancillary reagents and solvents required for either Boc or Fmoc peptide synthesis are commercially
available from various suppliers or can be prepared readily according to standard procedures. In addition, di- or other oligopeptides can be prepared readily according to standard procedures. In addition, automated peptide synthesizers with optimized, preprogrammed Boc and Fmoc synthesis cycles are available from numerous sources.


**General process conditions**

The following applies in general to all processes mentioned hereinbefore and hereinafter, while reaction conditions specifically mentioned above or below are preferred:

Functional groups in starting materials the reaction of which is to be avoided, especially carboxy, amino, hydroxy, mercapto and sulfo groups, can be protected by suitable protecting groups (conventional protecting groups) which are customarily used in the synthesis of peptide compounds, and also in the synthesis of cephalosporins and penicillins as well as nucleic acid derivatives and sugars. These protecting groups may already be present in the
precursors and are intended to protect the functional groups in question against undesired secondary reactions, such as acylation, etherification, esterification, oxidation, solvolysis, etc. In certain cases the protecting groups can additionally cause the reactions to proceed selectively, for example stereoselectively. It is characteristic of protecting groups that they can be removed easily, i.e. without undesired secondary reactions taking place, for example by solvolysis, reduction, photolysis, and also enzymatically, for example also under physiological conditions, and, especially, that they are not present in the end products.


When several protected functional groups are present, if desired the protecting groups can be so selected that more than one such group can be removed simultaneously, for example by acidolysis, such as by treatment with trifluoroacetic acid, or with hydrogen and a hydrogenation catalyst, such as a palladium-on-carbon catalyst. Conversely, the groups can also be so selected that they cannot all be removed simultaneously, but rather in a desired sequence, the corresponding intermediates being obtained.

In view of the close relationship between the compounds of formula I and their salts and starting materials (starting materials and intermediates) in free form and in the form of their salts, any reference hereinbefore and hereinafter to a free compound or a salt thereof is to be understood as meaning also the corresponding salt or free compound, respectively, where appropriate and expedient.
All the above-mentioned process steps can be carried out under reaction conditions that are known per se, preferably those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, preferably solvents or diluents that are inert towards the reagents used and are solvents therefor, in the absence or presence of catalysts, condensation agents or neutralising agents, for example ion exchangers, such as cation exchangers, e.g. in the H⁺ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from approximately -100°C to approximately 190°C, preferably from approximately -80°C to approximately 150°C, for example at from -80 to -60°C, at room temperature, at from -20 to 40°C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described under "Additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride, acid amides, such as dimethylformamide, bases, such as heterocyclic nitrogen bases, for example pyridine, carboxylic acid anhydrides, such as lower alkanic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.
The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallisation. Different crystalline forms may be present.

If necessary, protected starting materials may be used in all process steps and the protecting groups may be removed at suitable stages of the reaction.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. In the process of the present invention there are preferably used those starting materials which result in the compounds of formula I described at the beginning as being especially valuable. Special preference is given to reaction conditions that are analogous to those mentioned in the Examples.

**Pharmaceutical Compositions:**

The invention relates also to pharmaceutical compositions comprising compounds of formula I, to their use in the therapeutic (including prophylactic) treatment of the diseases mentioned above, to the compounds for said use and to the preparation of pharmaceutical preparations.

The pharmacologically acceptable compounds of the present invention may be used, for example, for the preparation of pharmaceutical compositions that comprise an effective amount of the active ingredient together or in admixture with a significant amount of inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

The invention relates also to a pharmaceutical composition that is suitable for administration to a warm-blooded animal, especially a human (or to cells or cell lines derived from a warm-blooded animal, especially a human, e.g. lymphocytes), for the treatment or preven-tion of (= prophylaxis against) a disease that responds to diseases that respond to inhibition of the interaction of proteins comprising SH2 domains and phosphoproteins, especially a
phosphorylated protein tyrosine kinase or modified versions thereof, preferably inhibition of the interaction of Grb2 SH2 with a phosphoprotein containing a \( \text{Tyr(PO_3H_2)} \cdot \text{X-Asn} \) motif, such as phosphorylated EGFR protein tyrosine kinase or modified derivatives thereof, but also other phospho-proteins such as SHC or modified derivatives thereof, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, which is effective for said inhibition, especially the inhibition of the interaction of Grb2 SH2 with a phosphoprotein containing a \( \text{Tyr(PO_3H_2)} \cdot \text{X-Asn} \) motif, such as phosphorylated EGFR protein tyrosine kinase or modified derivatives thereof, but also other phospho-proteins such as SHC, or truncated derivatives thereof, together with at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention are those for enteral, such as nasal, rectal or oral, or parenteral, such as intramuscular or intravenous, administration to warm-blooded animals (humans and animals), that comprise an effective dose of the pharmacologically active ingredient, alone or together with a significant amount of a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, the body weight, the age and the individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

The invention relates also to a method of treating diseases that respond to inhibition of the interaction of proteins comprising SH2 domains and phosphoproteins, especially the phosphorylated protein tyrosine kinases or modified versions thereof; preferably of Grb2 SH2 with a phospho-protein containing a \( \text{Tyr(PO_3H_2)} \cdot \text{X-Asn} \) motif, such as phosphorylated EGFR protein tyrosine kinase or modified derivatives thereof, but also other phospho-proteins such as SHC or modified derivatives thereof; which comprises administering a prophylactically or especially therapeutically effective amount of a compound of formula I according to the invention, especially to a warm-blooded animal, for example a human, that, on account of one of the mentioned diseases, requires such treatment. The dose to be administered to warm-blooded animals, for example humans of approximately 70 kg body weight, is from approximately 3 mg to approximately 30 g, preferably from approximately 10 mg to approximately 1.5 g, for example approximately from 100 mg to 1000 mg per person per day, divided preferably into 1 to 3 single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.
The pharmaceutical compositions comprise from approximately 1 % to approximately 95%, preferably from approximately 20 % to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional dissolving, lyophilising, mixing, granulating or confectioning processes.

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilised compositions that comprise the active ingredient alone or together with a carrier, for example mannitol, for such solutions or suspensions to be produced prior to use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting and/or emulsifying agents, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilising processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylc acid, myristic acid, pentadecylc acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brasilic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a mono- or poly-hydroxy, for example a mono-, di- or tri-hydroxy, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. The following examples of fatty acid esters are therefore to be mentioned: ethyl oleate, isopropyl
myristate, isopropyl palmitate, "Labrafac M 2375" (polyoxyethylene glycerol trioleate, Gattefossé, Paris), "Miglyol 812" (triglyceride of saturated fatty acids with a chain length of C<sub>8</sub> to C<sub>12</sub>, Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The injection compositions are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into ampoules or vials and sealing the containers.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragée cores or capsules. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes using for example corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, *inter alia*, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as ethylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Capsules are dry-filled capsules made of gelatin and soft sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired with stabilisers. In soft capsules the active ingredient is preferably dissolved
or suspended in suitable oily excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilisers and/or antibacterial agents to be added. Dyes or pigments may be added to the tablets or dragée coatings or the capsule casings, for example for identification purposes or to indicate different doses of active ingredient.

Examples

Embodiments of the invention are described in the following specific examples which are not to be construed to be intended to limit the scope of the invention in any way, but serve merely for illustration:

Temperatures, if not mentioned: room temperature/ambient temperature. In mixtures, relations of parts of solvent or eluent or reagent mixtures in liquid form are given as volume relations (v/v), if not indicated otherwise.

Symbols used for amino acids and peptides are in accordance with IUPAC-IUB Commission on Biochemical Nomenclature. If not mentioned otherwise, amino acids are always in the L-form. Other abbreviations used are:

Abbreviations: AcGlu: bivalent radical of 1-amino cyclopentane carboxylic acid (Aldrich, Buchs, Switzerland); AcGlu: bivalent radical of 1-amino cyclo-hexane carboxylic acid (Fluka, Buchs, Switzerland); Acm: acetamidomethyl; βAla: beta Alanyl = bivalent radical of 3-amino pro-pionic acid; Boc: tert-Butyloxycarbonyl; BOP: benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluoroborate; Dansyl: 5-dimethylamino-napthalenesulfonyl; Fmoc: fluorenylmethoxycarbonyl; Fmoc-PAL-PEG-PS (Millipore, Bedford, USA): a resin used for peptide synthesis; F2Pmp: 4-phosphono(difluoromethyl)-L-phenylalanine; HATU: N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide HOAc: acetic acid; HOBT: N-hydroxybenzotriazole; HPLC: high pressure liquid chromatography; HPLC System A is defined in Example 1; MBHA: 4-methylbenzhydryamine (resin component); PAL: trisalkyl- (= methyl)benzylamide linker; PEG: polyethylene glycol; Rf: ratio of fronts in thin layer chromatography employing silica gel plates (Merck, Darmstadt, FRG); TPTU: 2-(2-pyridon-1-yl)-1,1,3,3-tetramethylyuronium-tetrafluoroborate; tR: retention time in HPLC; Tyr(PO3H2): [4-(O-Phosphono)-Tyr].
**Example 1:** 2-Aminobenzoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gin-NH₂ (TFA salt)

(SEQ ID NO: 1)

The peptide is synthesized on a Milligen 9050 automated peptide synthesizer (continuous flow; Millipore, Bedford, MA, USA), starting with an Fmoc-PAL-PEG-PS resin (see Albericio, F. et al, J. Org. Chem., 55 (1990) 3730-3743) for establishing the C-terminal carboxamide, and using chemical protocols based on the fluorenlymethoxycarbonyl chemistry (see E. Atherton and R.C. Sheppard, in Solid-Phase Peptide Synthesis-A Practical Approach, ed.: D. Rickwood and B.D. Hames, IRL Press at Oxford University Press, Oxford, 1989). The required Fmoc-amino acids (3 equiv.) are coupled using their 2,4,5-trichlorophenyl esters (single coupling) with minimum reaction times of 30 min (see 9050 Plus PepSynthesizer, User’s Guide, Millipore Corporation, Bedford, MA, 1992). Double coupling with 2-(2-pyridon-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate (TPTU) is carried out for glutamic acid. The incorporation of Nα-Fmoc-Tyr(PO₃H₂)-OH (3 equiv.; see Ottinger, E.A, et al., Biochemistry 32, 4354 (1993)) is accomplished with benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate/N-hydroxybenzotriazole (1:1, 3 equiv.; first coupling) and N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylen]-N-methylmethanaminium hexafluorophosphate N-oxide (3 equiv.; second coupling) in the presence of diisopropylamine (6 equiv.). 2-amino benzoic acid (Fluka, Buchs, Switzerland) is incorporated with benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate/N-hydroxybenzotriazole (double coupling). Amino acid side chains are protected with the following groups: tert-butyl for glutamic acid; and trityl for asparagine and glutamine. The completed peptide resin is simultaneously deprotected and cleaved by treatment with trifluoroacetic acid:H₂O (95:5, v/v) for 3 h at room temperature. The filtrate from the cleavage reaction is precipitated in diisopropyl ether/petroleum ether (1:1, v/v, 0 °C), and the precipitate collected by filtration. The crude peptide is purified by medium-pressure liquid chromatography using a C₁₈-column eluted with an acetonitrile-water gradient containing 0.1 % of TFA (Merck* LICHROPREP RP-18, 15-25 μm bead diameter, reversed phase HPLC column material based on C₁₈-derivatized silicagel, Merck, Darmstadt, FRG; column length 46 cm, diameter 3.6 cm; flow rate 53.3 ml/min; detection at 215 nm). The title compound is obtained: Mass spectral analysis (matrix-assisted laser-desorption ionization time-of-flight mass spectrometry, MALDI-TOF) revealed a molecular mass within 0.1 % of the expected values (negative-ion mode): 862.9 (calc. 862.8.
C_{36}H_{49}N_{9}O_{14}P_{1}\). The purity of the peptide is verified by reversed-phase analytical HPLC on a Nucleosil C{18}-column (250 x 4 mm, 5 \mu m, 100 Å): linear gradient over 10 min of MeCN/0.09% TFA and H_{2}O/0.1% TFA from 1:49 to 3:2; flow rate 2.0 mL/min, detection at 215 nm (System A); single peak at t_{R}= 5.97 min.

The following examples are obtained in analogy to the title compound of Example 1, if not indicated otherwise:

**Example 2:** Dansyl-Glu-Tyr(PO_{3}H_{2})-Ile-Asn-Gln-NH_{2} (TFA salt)

(SEQ ID NO: 2)

S-dimethylaminonaphthalene-1-sulfochloride (Fluka, Buchs, Switzerland) (3 equiv.) is incorporated in the presence of diisopropylamine (6 equiv.) in N-methylpyrrolidin-2-one (2 h incubation at room temperature).

Mass spectral analysis (negative-ion mode): 977.0 (calc. 977.0, C_{41}H_{55}N_{9}O_{15}S_{1}P_{1}), t_{R}= 7.20 min (HPLC System A).

**Example 3:** 2-Aminobenzoyl-Pro-Glu-Tyr(PO_{3}H_{2})-Ile-Asn-NH_{2} (TFA salt)

(SEQ ID NO: 3)

The 2-aminobenzoic acid acid building block is used in unprotected form.

Title compound: Mass spectral analysis (negative-ion mode): 831.5 (calc. 831.8, C_{36}H_{48}N_{8}O_{13}P_{1}), t_{R}= 6.68 min (HPLC System A).

**Example 4:** 1-Aminocyclohexyl-carbonyl-Glu-Tyr(PO_{3}H_{2})-Ile-Asn-Gln-NH_{2}

(SEQ ID NO: 4)

The title compound is obtained after acylation with 1-N-tet-butoxycarbonyl-aminocyclohexyl-carboxylic acid and deprotection in analogy to Example 1. Title compound:

Mass spectral analysis (negative-ion mode): 869.2 (calc. 868.9, C_{36}H_{55}N_{9}O_{14}P_{1}), t_{R}= 5.13 min (HPLC System A).

The starting material is obtained as follows:

a) 1-(N-tet-Butoxycarbonyl-aminocyclohexyl)-carboxylic acid

To a solution of 1-aminocyclohexyl-carboxylic acid (0.72 g, 5 mmol; Fluka, Buchs, Switzerland) in 5% NaHCO_{3}/dioxane (1:1, v/v; 20 ml) is added Boc_{2}O (3.3 ml, 15 mmol)
and stirring is continued until completion of the reaction. The alkaline solution is
concentrated and extracted with petroleum ether (2x5 ml); the ether extracts are discarded.
The aqueous phase is acidified with a 5% solution of citric acid to pH 2-3 and extracted with
ethyl acetate (2x30 ml). The ethyl acetate extracts are pooled, washed with water (2x30 ml),
dried over anhydrous Na₂SO₄ and evaporated in vacuo. Rᵣ = 0.66 (chloro-

**Example 5:** 2-Aminobenzoyl-Cys(Acm)-Tyr(PO₃H₂)-Ile-Asn-Cys(Acm)-NH₂ (TFA salt)
(SEQ ID NO: 5)
N⁰-Fmoc-Cys(Acm)-OH is from Calbiochem-Novabiochem (Läufelfingen, Switzerland). The
2-aminobenzoic acid acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 954.4 (calc. 954.0, C₅₈H₅₄N₁₀O₁₃S₂P₁),
⁴tᵣ = 6.24 min (HPLC System A).

**Example 6:** 2-Aminobenzoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-NH₂ (TFA salt)
(SEQ ID NO: 6)
The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 734.3 (calc. 734.7, C₃₁H₄₁N₇O₁₂P₁),
⁴tᵣ = 5.38 min (HPLC System A).

**Example 7:** 4-Methoxybenzoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 7)
4-Methoxybenzoic acid is from Fluka, Buchs, Switzerland. Title compound:
Mass spectral analysis (negative-ion mode): 877.7 (calc. 877.8, C₃₇H₅₀N₈O₁₅P₁),
⁴tᵣ = 6.62 min (HPLC System A).

**Example 8:** 2-Amino-nicotinyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂ (TFA salt)
(SEQ ID NO: 8)
The amino group of the 2-aminonicotinic acid acid building block (2-aminopyridine-3-
carbonic acid; Fluka, Buchs, Switzerland) is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 863.9 (calc. 863.8, C₃₅H₄₈N₁₀O₁₄P₁),
⁴tᵣ = 4.94 min (HPLC System A).
Example 9: 3,5-Diaminobenzoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂ (TFA salt)

(SEQ ID NO: 9)

The amino groups of the 3,5-diaminobenzoic acid acid building block (3,5-diaminobenzoic acid; Fluka, Buchs, Switzerland) are protected with the Boc group as described for 1-(N-tert-butoxycarbonyl-amino-cyclohexyl)-carboxylic acid, Example 4a). Title compound: Rf = 0.66 (chloroform:methanol:water:acetic acid = 550:470:130:5, v/v/v/v).

Mass spectral analysis (negative-ion mode): 877.6 (calc. 877.8, C₃₆H₅₀N₁₀O₁₄P₁), tᵣ= 4.76 min (HPLC System A).

Example 10: 2-Aminobenzoyl-Gln-Tyr(PO₃H₂)-Glu-Glu-Ile-NH₂ (TFA salt)

(SEQ ID NO: 10)

The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound:

Mass spectral analysis (negative-ion mode): 877.9 (calc. 877.8, C₃₇H₅₀N₈O₁₅P₁), tᵣ= 5.86 min (HPLC System A).

Example 11: 2-Aminobenzoyl-Pro-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂ (TFA salt)

(SEQ ID NO: 11)

The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound:

Mass spectral analysis (negative-ion mode): 830.6 (calc. 830.8, C₃₆H₄₉N₉O₁₂P₁), tᵣ= 6.55 min (HPLC System A).

Example 12: 3-Amino-2-naphthoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂ (TFA salt)

(SEQ ID NO: 12)

The amino group of the 3-amino-2-naphthoic acid (Fluka, Buchs, Switzerland) is used in unprotected form. Title compound: Mass spectral analysis (negative-ion mode): 913.0 (calc. 912.9, C₄₀H₅₁N₉O₁₄P₁), tᵣ= 6.24 min (HPLC System A).

Example 13: 2-Aminobenzoyl-Cys(Acm)-Tyr(PO₃H₂)-Ile-Asn-Gln-Cys(Acm)-NH₂ (TFA salt)

(SEQ ID NO: 13)

The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound:

Mass spectral analysis (negative-ion mode): 1082.8 (calc. 1082.2, C₄₃H₅₂N₁₂O₁₅S₂P₁), tᵣ= 6.01 min (HPLC System A).
Example 14: 2-Aminobenzoyl-Cys(Acm)-Tyr(PO₃H₂)-Cys(Acm)-Asn-Gln-NH₂ (TFA salt)
(SEQ ID NO: 14)
The 2-aminobenzoic acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 968.6 (calc. 969.0, C₃₇H₅₁N₁₁O₁₄S₂P₁),
tᵣ= 5.09 min (HPLC System A).

Example 15: 2-Aminobenzoyl-Cys(Acm)-Tyr(PO₃H₂)-Ile-Asn-D-Cys(Acm)-NH₂ (TFA salt)
(SEQ ID NO: 15)
The 2-aminobenzoic acid building block is used in unprotected form. N°-Fmoc-D-
Cys(Acm)-OH is from Novabiochem, Läufelfingen, Switzerland. Title compound:
Mass spectral analysis (negative-ion mode): 954.6 (calc. 954.0, C₃₈H₅₄N₁₀O₁₃S₂P₁),
tᵣ= 6.22 min (HPLC System A).

Example 16: 2-Aminobenzoyl-Asp-Tyr(PO₃H₂)-Ile-Ile-NH₂ (TFA salt)
(SEQ ID NO: 16)
The 2-aminobenzoic acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 719.7 (calc. 719.7, C₃₂H₄₄N₆O₁₁P₁),
tᵣ= 6.82 min (HPLC System A).

Example 17: 2-Aminobenzoyl-Asp-Tyr(PO₃H₂)-Ile-Ile-Pro-NH₂ (TFA salt)
(SEQ ID NO: 17)
The 2-aminobenzoic acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 816.5 (calc. 816.8, C₃₇H₅₁N₇O₁₂P₁),
tᵣ= 6.90 min (HPLC System A).

Example 18: 2-Aminobenzoyl-Ala-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂ (TFA salt)
(SEQ ID NO: 18)
The 2-aminobenzoic acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 805.1 (calc. 804.8, C₁₄H₃₇N₉O₁₂P₁),
tᵣ= 6.87 min (HPLC System A).

Example 19: 2-Aminobenzoyl-βAla-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂ (TFA salt)
(SEQ ID NO: 19)
The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 805.0 (calc. 804.8, C_{34}H_{47}N_{9}O_{12}P_{1}),
$t_R$ = 6.20 min (HPLC System A).

**Example 20:** 2-Aminobenzoyl-Gly-Tyr(PO_3H_2)-Ile-Asn-Gln-NH$_2$ (TFA salt)
(SEQ ID NO: 20)
The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 790.8 (calc. 790.8, C_{33}H_{45}N_{9}O_{12}P_{1}),
$t_R$ = 6.50 min (HPLC System A).

**Example 21:** 2-Aminobenzoyl-Leu-Tyr(PO_3H_2)-Ile-Asn-Gln-NH$_2$ (TFA salt)
(SEQ ID NO: 21)
The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 846.8 (calc. 846.9, C_{37}H_{53}N_{9}O_{12}P_{1}),
$t_R$ = 8.80 min (HPLC System A).

**Example 22:** 2-Aminobenzoyl-Val-Tyr(PO_3H_2)-Ile-Asn-Gln-NH$_2$ (TFA salt)
(SEQ ID NO: 22)
The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound:
Mass spectral analysis (negative-ion mode): 833.1 (calc. 832.8, C_{36}H_{51}N_{9}O_{12}P_{1}),
$t_R$ = 7.93 min (HPLC System A).

**Example 23:** 3-Aminobenzoyl-Glu-Tyr(PO_3H_2)-Ile-Asn-Gln-NH$_2$ (TFA salt)
(SEQ ID NO: 23)
The peptide is synthesized manually on a 4-(2',4'-dimethoxyphenyl-aminomethyl)-phenoxy-resin (Novabiochem, Läufelfingen, Switzerland), employing the fluorenylmethoxycarbonyl strategy. Fmoc-removal is with piperidine/dimethylacetamide (1:4, v/v; 6 x 2 min), followed by washing with methanol (3 x 1 min), N-methylpyrrolidin-2-one (2 x 1 min), methanol (3 x 1 min), and N-methylpyrrolidin-2-one (3 x 2 min). Coupling is achieved by first dissolving the Fmoc-amino acid (2 equiv.), diisopropylethylamine (2.2 equiv.), and the 2-(2-pyridon-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate reagent (2 equiv.) in N-methylpyrrolidin-2-one, then waiting 3 min for preactivation, adding the mixture to the resin, and finally shaking for at least 45 min. Amino acid side chains are protected with the following groups: tert-butyl for
glutamic acid; and trityl for asparagine and glutamine. The incorporation of N\textalpha-Fmoc-
Tyr(PO$_3$H$_2$)-OH (3 equiv.) is accomplished with benzotriazole-1-yl-oxy-tris-(dimethylamino)-
phosphoniumhexafluorophosphate/N-hydroxybenzotriazole (1:1; 3 equiv.; first coupling) in
the presence of diisopropylethylamine (7 equiv.) and N-[(dimethylamino)-1H-1,2,3-triazole-
[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide (3
equiv., second coupling) in the presence of diisopropylethylamine (7 equiv.). 3-(N-tert-But-
oxycarbonyl-amino)benzoic acid (3 equiv.) is coupled with BOP/HOBt (1:1; 3 equiv.; first
coupling) in the presence of diisopropylethylamine (6 equiv.) and TPTU/HOBt (1:1; 3 equiv.
second coupling,) in the presence of diisopropylamine (6 equiv.). The complete peptide
resin obtained after the last coupling step is simultaneously deprotected and cleaved by
treatment with trifluoroacetic acid/H$_2$O (95:5, v/v) for 3 h at room temperature. The filtrate
from the cleavage reaction is precipitated in diisopropyl ether/petroleum ether (1:1, v/v, 0
°C), and the precipitate collected by filtration. The crude peptide is purified by medium-
pressure liquid chromatography as described in Example 1. Title compound: Mass spectral
analysis (negative-ion mode): 862.4 (calc. 862.8, C$_{36}$H$_{49}$N$_9$O$_{14}$P$_1$), t$_R$= 4.81 min (HPLC
System A).

The starting material is obtained as follows:

a) 3-(N-tert-Butoxycarbonyl-amino)-benzoic acid
The title compound is synthesized as indicated for 1-(N-tert-butoxycarbonyl-aminocyclo-
hexyl)-carboxylic acid (Example 4a)), starting from 3-aminobenzoic acid (Fluka, Buchs,

**Example 24:** 4-Aminobenzoyl-Glu-Tyr(PO$_3$H$_2$)-Ile-Asn-Gln-NH$_2$ (TFA salt)
(SEQ ID NO: 24)
Mass spectral analysis (negative-ion mode): 862.6 (calc. 862.8, C$_{36}$H$_{49}$N$_9$O$_{14}$P$_1$), t$_R$=
4.95 min (HPLC System A).

The starting material is obtained as follows:

a) N-4-tert-Butoxycarbonyl-amino-benzoic acid
The title compound is synthesized as described for 1-(N-tert-butoxycarbonyl-aminocyclohexyl)-carboxylic acid (Example 4 a)). \( R_f = 0.4 \) (chloroform:methanol:water:acetic acid = 850:130:15:5, v/v/v/v/v).

**Example 25**: Isoquinoline-1-ylcarbonyl-Glu-Tyr(PO\(_3\)H\(_2\))-Ile-Asn-Gln-NH\(_2\)
(SEQ ID NO: 25)
Isoquinoline-1-carboxylic acid is from Fluka, Buchs, Switzerland. Title compound: Mass spectral analysis (negative-ion mode): 899.0 (calc. 898.9, C\(_{39}\)H\(_{49}\)N\(_9\)O\(_{14}\)P\(_1\)), \( t_R = 6.59 \) min (HPLC System A).

**Example 26**: Quinoline-3-ylcarbonyl-Glu-Tyr(PO\(_3\)H\(_2\))-Ile-Asn-Gln-NH\(_2\)
(SEQ ID NO: 26)
Quinoline-3-carboxylic acid is from Fluka, Buchs, Switzerland. Title compound: Mass spectral analysis (negative-ion mode): 899.3 (calc. 898.9, C\(_{39}\)H\(_{49}\)N\(_9\)O\(_{14}\)P\(_1\)), \( t_R = 5.66 \) min (HPLC System A).

**Example 27**: Quinoline-2-ylcarbonyl-Glu-Tyr(PO\(_3\)H\(_2\))-Ile-Asn-Gln-NH\(_2\)
(SEQ ID NO: 27)
Quinoline-2-carboxylic acid is from Fluka, Buchs, Switzerland. Title compound: Mass spectral analysis (negative-ion mode): 898.9 (calc. 898.9, C\(_{39}\)H\(_{49}\)N\(_9\)O\(_{14}\)P\(_1\)), \( t_R = 7.13 \) min (HPLC System A).

**Example 28**: Quinoline-4-ylcarbonyl-Glu-Tyr(PO\(_3\)H\(_2\))-Ile-Asn-Gln-NH\(_2\)
(SEQ ID NO: 28)
Quinoline-2-carboxylic acid is from Fluka, Buchs, Switzerland. Title compound: Mass spectral analysis (negative-ion mode): 898.9 (calc. 898.9, C\(_{39}\)H\(_{49}\)N\(_9\)O\(_{14}\)P\(_1\)), \( t_R = 5.22 \) min (HPLC System A).

**Example 29**: 2-Aminobenzoyl-Ile-Tyr(PO\(_3\)H\(_2\))-Ile-Asn-Gln-NH\(_2\) (TFA salt)
(SEQ ID NO: 29)
The 2-aminobenzoic acid acid building block is used in unprotected form. Title compound: Mass spectral analysis (negative-ion mode): 846.8 (calc. 846.9, C\(_{37}\)H\(_{53}\)N\(_9\)O\(_{12}\)P\(_1\)), \( t_R = 8.60 \) min (HPLC System A).
Example 30: Quinoline-8-ylsulfonyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 30)
8-Quinolinesulfonfyl chloride (3 equiv.; Fluka, Buchs, Switzerland)) is incorporated to the peptide resin intermediate in the presence of diisopropylethylamine (6 equiv.) in N- methylpyrrolidin-2-one. Title compound: Mass spectral analysis (negative-ion mode): 934.9 (calc. 934.9, C₃₈H₄₉N₉O₁₅S₁P₁), tᵣ= 6.49 min (HPLC System A).

Example 31: (+/-)-Indoline-2-ylcarbonyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 31)
The unprotected (+/-)-Indoline-2-ylcarboxylic acid used is from Fluka, Buchs, Switzerland. Title compound: Mass spectral analysis (negative-ion mode): 899.0 (calc. 888.9, C₃₈H₅₁N₉O₁₄P₁), tᵣ= 5.99 min (HPLC System A).

Example 32: Indole-2-ylcarbonyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 32)
The unprotected Indole-2-yl carboxylic acid used is from Fluka, Buchs, Switzerland. Title compound: Mass spectral analysis (negative-ion mode): 886.9 (calc. 886.8, C₃₈H₄₉N₉O₁₄P₁), tᵣ= 7.40 min (HPLC System A).

Example 33: Indole-3-ylcarbonyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 33)
The unprotected Indole-3-ylcarboxylic acid used is from Fluka, Buchs, Switzerland. Title compound: Mass spectral analysis (negative-ion mode): 886.8 (calc. 886.8, C₃₈H₄₉N₉O₁₄P₁), tᵣ= 6.50 min (HPLC System A).

Example 34: 3-Aminopyrazine-2-ylcarbonyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂ (TFA salt)
(SEQ ID NO: 34)
The amino group of the 3-aminopyrazine-2-ylcarboxylic acid building block (Fluka, Buchs, Switzerland) is unprotected. Title compound: Mass spectral analysis (negative-ion mode): 865.0 (calc. 864.8, C₃₄H₄₁N₁₁O₄P₁). Linear gradient over 10 min of MeCN/0.09% TFA and H₂O/0.1% TFA from 5:95 to 13:7, flow rate 1.5 ml/min, detection at 215 nm: tᵣ= 5.73 min (HPLC System B).
Example 35: 2-Aminobenzoyl-Glu-F2Pmp-Ile-Asn-Gln-NH2 (TFA salt)
(SEQ ID NO: 35)
The peptide derivative is synthesized manually using the 4-(2',4'-dimethoxyphenyl-aminomethyl)-phenoxy-resin Novabiochem, Läufelfingen, Switzerland), employing a procedure analogous to Example 23. Incorporation of N\textsuperscript{\textbeta}-Fmoc-[4-(O-diethyl)-phosphono-(difluoromethyl)]-L-phenylalanine (synthesis see Tetrahedron Lett. 34(22), 3543 (1993)) to the protected peptide resin is carried out with BOP/HOBt (1:1; 3 equiv.) in the presence of diisopropylethylamine (7 equiv.), with 3 h reaction time. After completion of the synthesis of the full peptide, the protected peptide resin is treated with 1 M trimethylsilyl trifluoromethane sulfonate-2 M dimethylsulfide-trifluoroacetic acid (500 \(\mu\)l to 0.005 mmol of NH\textsubscript{2})-ethane-dithiol (100 \(\mu\)l)-m-cresol (25 \(\mu\)l) 30 min at 4 \(^\circ\)C and 3.5 h at room temperature (see Tetrahedron Lett. 34(44), 7039 (1993)). The filtrate from the cleavage reaction is precipitated in diisopropyl ether-petroleum ether (1:1, v/v, 0 \(^\circ\)C), and the precipitate collected by filtration. The crude peptide is purified by medium-pressure liquid chromatography as described in Example 1, and the title compound is obtained: Mass spectral analysis (negative-ion mode): 896.8 (calc. 896.8, C\textsubscript{37}H\textsubscript{49}N\textsubscript{9}O\textsubscript{13}F\textsubscript{2}P\textsubscript{1}), \(t_R= 5.40 \) min (HPLC System A).

Example 36: 3-Aminobenzoyl-Glu-F2Pmp-Ile-Asn-Gln-NH2 (TFA salt)
(SEQ ID NO: 36)
The amino group of the 3-aminobenzoic acid building block is protected with the tert-butoxycarbonyl group as described in Example 23 a). The title compound is prepared using a procedure analogous to Example 35: Mass spectral analysis (negative-ion mode): 896.2 (calc. 896.8, C\textsubscript{37}H\textsubscript{49}N\textsubscript{9}O\textsubscript{13}F\textsubscript{2}P\textsubscript{1}). Linear gradient over 10 min of MeCN/0.09% TFA and H\textsubscript{2}O/0.1% TFA from 5.95 to 13.7, flow rate 1.5 mL/min, detection at 215 nm. \(t_R= 5.48 \) min (HPLC System B).

Example 37: 2-Aminobenzoyl-Cys-Tyr(Po\textsubscript{3}H\textsubscript{2})-Ile-Asn-Cys-NH2 (TFA salt)

\[
\begin{array}{c}
|\text{S}|
|\text{S}|
\end{array}
\]

(SEQ ID NO: 37)
Iodine (6 equiv.) is added to a solution of 2-aminobenzoyl-Cys(Acm)-Tyr(Po\textsubscript{3}H\textsubscript{2})-Ile-Asn-Cys(Acm)-NH\textsubscript{2} (Example 5) in HOAc/H\textsubscript{2}O (8:2, v/v) (36.0 mg in 35 ml). Aliquots of the
solution are removed at different times, quenched with a saturated solution of ascorbic acid, and then analyzed by analytical HPLC. After 30 min, additional iodine (6 equiv.) is added.

After disappearance of the starting material, the reaction is quenched by addition of a 5% solution of ascorbic acid in water. The reaction mixture is concentrated and injected directly in a medium-pressure liquid chromatography system as described in Example 1, and the title compound is obtained: Mass spectral analysis (negative-ion mode): 809.7 (calc. 809.8, C_{32}H_{42}N_{8}O_{11}S_{2}P_{1}), t_{R} = 5.62 min (HPLC System A).

**Example 38:** 2-Aminobenzoyl-Cys-Tyr(PO_{3}H_{2})-Ile-Asn-Gln-Cys-NH_{2} (TFA salt)

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S-----------------------------------S
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(SEQ ID NO: 38)

The compound is prepared using a procedure analogous to Example 37, starting from the title compound of Example 13. Title compound: Mass spectral analysis (negative-ion mode): 938.7 (calc. 938.0, C_{37}H_{50}N_{10}O_{13}S_{2}P_{1}), t_{R} = 6.27 min (HPLC System A).

**Example 39:** 2-Aminobenzoyl-Cys-Tyr(PO_{3}H_{2})-Cys-Asn-Gln-NH_{2} (TFA salt)

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  |  
S-----------------------------S
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(SEQ ID NO: 39)

The compound is prepared using a procedure analogous to Example 37, starting from the title compound of Example 14. Title compound: Mass spectral analysis (negative-ion mode): 825.5 (calc. 824.8, C_{31}H_{39}N_{9}O_{12}S_{2}P_{1}), t_{R} = 6.32 min (HPLC System: Same column as for HPLC System A, using a linear gradient over 10 min of acetonitrile/0.09% TFA and H_{2}O/0.1% TFA from 1:49 to 3:7, flow rate 2.0 ml/min, detection at 215 nm).

**Example 40:** 2-Aminobenzoyl-Cys-Tyr(PO_{3}H_{2})-Ile-Asn-D-Cys-NH_{2} (TFA salt)

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(SEQ ID NO: 40)

The compound is prepared using a procedure analogous to that in Example 37, starting from the title compound of Example 15. Title compound: Mass spectral analysis (negative-ion mode): 809.7 (calc. 809.8, C_{32}H_{42}N_{8}O_{11}S_{2}P_{1}), t_{R} = 5.78 min (HPLC System A).
Example 41: 2-Hydroxy-benzyoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂

(SEQ ID NO: 41)

The peptide is synthesized on a Millipore 9050 Plus peptide synthesizer in analogy to the method described in Example 1. The hydroxyl group of the 2-hydroxybenzoic acid (Fluka, Buchs, Switzerland) is not protected- Double coupling with BOP/HOBt (1:1, 3.0 equiv.). Title compound: Mass spectral analysis (negative-ion mode): 863.5 (calc. 863.8, C₃₆H₄₈N₈O₁₅P₁). HPLC (same column as HPLC System A): Linear gradient over 10 min of MeCN/0.09% TFA and H₂O/0.1% TFA from 1:19 to 1:0, flow rate 2.0 ml/min, detection at 215 nm; t₁₁ = 5.41 min.

Example 42: 2-Aminobenzoyl-Glu-Tyr(PO₃H₂)-Ac₅-C-Asn-NH₂

(SEQ ID NO: 42)

The title compound is obtained in analogy to Example 23. Fmoc-1-amino-1-cyclopentane-carboxylic acid (2 equiv.) is coupled with BOP/HOBt (1:1, 2 equiv.; first coupling) and HATU (2 equiv.; second coupling) in the presence of diisopropylamine. Title compound: Mass spectral analysis (negative-ion mode): 732.8 (calc. 732.7, C₃₁H₃₈N₇O₁₂P₁); t₁₁ = 5.33 (HPLC System A).

The starting material is obtained as follows:

a) Fmoc-1-amino-1-cyclopentane-carboxylic acid


Example 43: 2-Aminobenzoyl-Glu-Tyr(PO₃H₂)-Ac₅-C-Asn-NH₂

(SEQ ID NO: 43)

The title compound is obtained in analogy to Examples 23. Fmoc-1-amino-1-cyclohexane-carboxylic acid (2 equiv.) is coupled with BOP/HOBt (1:1, 2 equiv.; first coupling) and HATU (2 equiv.; second coupling) in the presence of diisopropylamine. Title compound: Mass spectral analysis (negative-ion mode): 747.0 (calc. 746.7, C₃₂H₄₁N₇O₁₂P₁); t₁₁ = 5.33 (HPLC System A).
The starting material is obtained as follows:

a) Fmoc-1-amino-1-cyclohexanecarboxylic acid

In analogy to the processes mentioned above, the following compound of Example 44 is synthesized:

**Example 44:** 2-Aminobenzoyl-Phe-Tyr(PO3H2)-Ile-Asn-NH2 (TFA salt)
(SEQ ID NO: 44)
Title compound: Mass spectral analysis (negative-ion mode): 753.2 (calc. 752.8, \( C_{35}H_{43}N_7O_{10}P_1 \), \( t_R = 7.07 \) min (HPLC System A)

**Example 45:** Gelatine solution:
A sterile-filtered aqueous solution, with 20 % cyclodextrins as solubilisers, of one of the compounds of formula I mentioned in the preceding Examples (e.g. Example 1) as active ingredient, is so mixed under aseptic conditions, with heating, with a sterile gelatine solution containing phenol as preservative, that 1.0 ml of solution has the following composition:

- active ingredient: 3 mg
- gelatine: 150.0 mg
- phenol: 4.7 mg
- dist. water with 20 % cyclodextrins as solubilisers: 1.0 ml

**Example 46:** Sterile dry substance for injection:
5 mg of one of the compounds of formula I mentioned in the preceding Examples (e.g. Example 1) as active ingredient are dissolved in 1 ml of an aqueous solution with 20 mg of mannitol and 20 % cyclodextrins as solubilisers. The solution is sterile-filtered and introduced under aseptic conditions into a 2 ml ampoule, deep-frozen and lyophilised.
Before use, the lyophilisate is dissolved in 1 ml of distilled water or 1 ml of a physiological saline solution. The solution is administered intramuscularly or intravenously. This formulation can also be introduced into a twin-chambered injection ampoule.

**Example 47: Nasal spray:**
500 mg of finely ground (<5.0 μm) powder of one of the compounds of formula I mentioned in the preceding Examples (e.g. Example 1) is suspended as active ingredient in a mixture of 3.5ml of Mygylol 812® and 0.08 g of benzyl alcohol. The suspension is introduced into a container having a metering valve. 5.0 g of Freon 12® are introduced under pressure into the container through the valve. The *"Freon"* is dissolved in the Mygylol/benzyl alcohol mixture by shaking. The spray container contains approximately 100 single doses which can be administered individually.

**Example 48: Film-coated tablets**
The following ingredients are used for the preparation of 10000 tablets each containing 100 mg of active ingredient:

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<tr>
<th>Ingredient</th>
<th>Amount</th>
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<td>sodium carboxymethyl starch</td>
<td>250 g</td>
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<tr>
<td>water</td>
<td>quantum satis</td>
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</table>

A mixture of one of the compounds of formula I mentioned in the preceding Examples (e.g. Example 1) as active ingredient, 50 g of corn starch and the colloidal silica is processed with a starch paste, made from 250 g of corn starch and 2.2 kg of demineralised water, to form a moist mass. This is forced through a sieve having a mesh size of 3 mm and dried at 45° for 30 min in a fluidised bed drier. The dry granules are pressed through a sieve having a mesh size of 1 mm, mixed with a pre-sieved mixture (1 mm sieve) of 330 g of corn starch, the magnesium stearate, the stearic acid and the sodium carboxymethyl starch, and compressed to form slightly biconvex tablets.
Example 49: Incubation of phosphotyrosine protein immobilized on a solid phase with a chimeric SH2-GST (GST = glutathione S-transferase) protein in the presence of a test substance

Using the test system mentioned above, and using the phosphorylated “tail” EGFR-MBP fusion protein as ligand, the following IC<sub>50</sub> values are obtained:

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
   (A) NAME: CIBA-GEIGY AG
   (B) STREET: Klybeckstr. 141
   (C) CITY: Basel
   (E) COUNTRY: Switzerland
   (F) POSTAL CODE (ZIP): 4002
   (G) TELEPHONE: +41 61 69 11 11
   (H) TELEFAX: + 41 61 696 79 76
   (I) TELEX: 962 991

(ii) TITLE OF INVENTION: Various acylated oligopeptides

(iii) NUMBER OF SEQUENCES: 44

(iv) COMPUTER READABLE FORM:
   (A) MEDIUM TYPE: Floppy disk
   (B) COMPUTER: IBM PC compatible
   (C) OPERATING SYSTEM: PC-DOS/MS-DOS
   (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

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   (D) TOPOLOGY: linear

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   (D) TOPOLOGY: linear

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1  5

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(ix) FEATURE:
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   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Ile-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Xaa Xaa Glu Glu Xaa

1     5

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Xaa Xaa Ile Asn Xaa

1 5

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product=

"N-(3-amino-2-naphthoyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"
(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Xaa Xaa Ile Asn Xaa
1 5

(ii) MOLECULE TYPE: peptide

(iii) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-S-acetylaminoethyl-Cys"

(iv) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(v) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION:/product= ""
"S-(acetylaminomethyl)-Cys-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Xaa Xaa Ile Asn Gln Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 1
   (D) OTHER INFORMATION:/product=
      "N-(2-aminobenzoyl)-S-acetylaminomethyl-Cys"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 2
   (D) OTHER INFORMATION:/product= "(O-phosphonyl-L-Tyr)"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 3
   (D) OTHER INFORMATION:/product=
      "S-(acetylaminomethyl)-Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Xaa Xaa Xaa Asn Xaa
1   5

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product=
   "N-(2-aminobenzoyl)-S-acetylaminoethyl-Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product=
   "S-(acetylaminoethyl)-D-Cys"
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Xaa Xaa Ile Asn Xaa
1  5

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:4
(D) OTHER INFORMATION:/product= "Ile-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Xaa Xaa Ile Xaa
(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:1
   (D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Asp"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:2
   (D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:5
   (D) OTHER INFORMATION:/product= "Pro-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Xaa Xaa Ile Ile Xaa

1  5

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Ala"

(ix) FEATURE:
(A) NAME/KEY: Active-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:
Xaa Xaa Ile Asn Xaa
1  5

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-bAla"
   /note= "bAla is beta-Alanyl (-NH-CH2-CH2-(C=O)-)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Xaa Glu Xaa Ile Asn Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "N-(2-aminobenzoyl)-Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Xaa Xaa Ile Asn Xaa

1  5

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "N-(2-aminobenzoyl)-Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Xaa Xaa Ile Asn Xaa
  1  5

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Xaa Xaa Ile Asn Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(3-aminobenzoyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Xaa Xaa Ile Asn Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(4-aminobenzoyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(x) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Xaa Xaa Ile Asn Xaa
1 5
(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:1
   (D) OTHER INFORMATION:/product="N-(isoquinoline-1-ylcarbonyl)-Glu"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:2
   (D) OTHER INFORMATION:/product="(O-phosphono-L-Tyr)"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:5
   (D) OTHER INFORMATION:/product="Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Xaa Xaa Ile Asn Xaa

1 5

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(quinoline-3-ylcarbonyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Xaa Xaa Ile Asn Xaa

1 5

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:1
   (D) OTHER INFORMATION:/product=  
       "N-(quinoline-2-yl-carbonyl)-Glu"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:2
   (D) OTHER INFORMATION:/product= 
       "(O-phosphono-L-Tyr)"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:5
   (D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Xaa Xaa Ile Asn Xaa
1  5

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "N-(quinoline-4-ylcarbonyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Xaa Xaa Ile Asn Xaa

1  5

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "N-(2-aminobenzoyl)-Ile"
(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION::/product= 
"(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION::/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Xaa Xaa Ile Asn Xaa

1 5

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION::/product=
"N-(quinoline-8-ylsulfonyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION::/product= "(O-phosphono-L-Tyr)"
(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 5
   (D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Xaa Xaa Ile Asn Xaa
  
1     5

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 1
   (D) OTHER INFORMATION:/product=
       "N-(indoline-2-y1carbonyl)-Glu"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 2
   (D) OTHER INFORMATION:/product= "O-phosphono-L-Tyr"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 5
(D) OTHER INFORMATION: /product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:
Xaa Xaa Ile Asn Xaa
1  5

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:1
(D) OTHER INFORMATION: /product= "N-(indole-2-yl-carbonyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:2
(D) OTHER INFORMATION: /product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:5
(D) OTHER INFORMATION: /product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:
Xaa Xaa Ile Asn Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 5 amino acids
    (B) TYPE: amino acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
    (A) NAME/KEY: Modified-site
    (B) LOCATION: 1
    (D) OTHER INFORMATION:/product= "N-(indole-3-ylcarbonyl)-Glu"

(ix) FEATURE:
    (A) NAME/KEY: Modified-site
    (B) LOCATION: 2
    (D) OTHER INFORMATION:/product= "O-phosphono-L-Tyr"

(ix) FEATURE:
    (A) NAME/KEY: Modified-site
    (B) LOCATION: 5
    (D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Xaa Xaa Ile Asn Xaa
1 5
(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:1
(D) OTHER INFORMATION:/product= "N-(3-aminopyrazine-2-ylcarbonyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Xaa Xaa Ile Asn Xaa

1  5

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single

(D) **TOPOLOGY:** linear

(ii) **MOLECULE TYPE:** peptide

(ix) **FEATURE:**

(A) **NAME/KEY:** Modified-site

(B) **LOCATION:** 1

(D) **OTHER INFORMATION:** /product= "N-(2-aminobenzoyl)-Glu"

(ix) **FEATURE:**

(A) **NAME/KEY:** Modified-site

(B) **LOCATION:** 2

(D) **OTHER INFORMATION:** /product= "4-(phosphono-difluormethyl)-Phe"

(ix) **FEATURE:**

(A) **NAME/KEY:** Modified-site

(B) **LOCATION:** 5

(D) **OTHER INFORMATION:** /product= "Gln-NH2"

(xi) **SEQUENCE DESCRIPTION:** SEQ ID NO: 35:

Xaa Xaa Ile Asn Xaa

1 5

(2) **INFORMATION FOR SEQ ID NO: 36:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 5 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single

(D) **TOPOLOGY:** linear
(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(3-aminobenzoyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "4-(phosphono-difluormethyl)-Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Xaa Xaa Ile Asn Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Cys"
    /note= "The sulfur from the Cys in 1-position and the sulfur from the Cys in 5-position together form a disulfide bridge"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Cys-NH2"
    /note= "the sulfur from the Cys in 5-position and the sulfur from the Cys in 1-position together form a disulfide bridge"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Xaa Xaa Ile Asn Xaa
1  5

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 6 amino acids
    (B) TYPE: amino acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
    (A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Cys"
   /note= "the sulfur from the Cys in 1-position and the sulfur
   from the Cys in 6-position together form a disulfide bridge"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 2
   (D) OTHER INFORMATION:/product= "(O-phospho-L-Tyr)"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 6
   (D) OTHER INFORMATION:/product= "Cys-NH2"
   /note= "The sulfur from the Cys in 6-position and the sulfur
   from the Cys in 1-position together form a disulfide bridge"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Xaa Xaa Ile Asn Gln Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: both

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Cys"
   /note= "The sulfur from the Cys in 1-position and the sulfur
   from the Cys in 3-position together form a disulfide bond"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:2
   (D) OTHER INFORMATION:/product= "O-phosphono-L-Tyr"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:5
   (D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Xaa Xaa Cys Asn Xaa
   1  5

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:1
   (D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Cys"
   /note= "The sulfur from the Cys in 1-position and the sulfur
   from the D-Cys in 5-position together form a disulfide bond"
(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:2
   (D) OTHER INFORMATION:/product="(O-phosphono-L-Tyr)"

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:5
   (D) OTHER INFORMATION:/product="D-Cys-NH2"
       /note= "The sulfur from the D-Cys in 5-position and the sulfur
       from the Cys in 1-position together form a disulfide bridge"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

Xaa Xaa Ile Asn Xaa

1  5

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 5 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION:1
   (D) OTHER INFORMATION:/product="N-(2-hydroxybenzoyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION:/product= "Gln-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Xaa Xaa Ile Asn Xaa
1  5

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphono-L-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4
(D) OTHER INFORMATION:/product= "Asn-NH2"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION:/product=
   "1-(imino)-cyclopentan-1-ylcarbonyl"
   /note= "Bivalent Moiety of 1-amino-cylopentane-1-carboxylic acid
   (bonded N-terminally via the 1-imino resulting from the 1-amino
   group and C-terminally via the 1-carbonyl resulting from the
   1-carboxy group)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Xaa Xaa Xaa Xaa

1

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 4 amino acids
   (B) TYPE: amino acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
   (A) NAME/KEY: Modified-site
   (B) LOCATION: 1
   (D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Glu"

(ix) FEATURE:
(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION:/product= "(O-phosphonomethyl-Tyr)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION:/product=
    "1-(imino)-cyclohexyl-1-carbonyl"
    /note= "bivalent radical of 1-amino-cyclohexyl-1-carboxylic acid"
    (bound N-terminally via the 1-imino of its 1-amino group and
    C-terminally via the 1-carbonyl of its 1-carboxy group)"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4
(D) OTHER INFORMATION:/product= "Asn-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Xaa Xaa Xaa Xaa

1

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 4 amino acids
    (B) TYPE: amino acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1

(D) OTHER INFORMATION:/product= "N-(2-aminobenzoyl)-Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2

(D) OTHER INFORMATION:/product= "(O-P-Tyr)"
   /note= "O-P-Tyr stands for O-Phosphono-L-Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4

(D) OTHER INFORMATION:/product= "Asn-NH2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Xaa Xaa Ile Xaa

1
What is claimed is

1. A compound of formula I

   \[ X - A - B - PTI - (AA)_m - Y \] (I)

   wherein

   m is 2 to 15,

   X is arylcarbonyl, arylsulfonyl, cycloalkylcarbonyl, cycloalkanesulfonyl, heterocyclylcarbonyl or heterocyclylsulfonyl;

   A is absent or the bivalent radical of a natural or unnatural amino acid,

   B is the bivalent radical of a natural amino acid,

   PTI is the bivalent radical of phosphotyrosine or a phosphotyrosine mimic,

   AA stands for a bivalent radical of a natural or unnatural amino acid, and

   Y is hydroxy, a C-terminal protecting group or a primary, secondary or tertiary amino group,

   with the proviso that two or more sulfhydryl groups belonging to any amino acid A, B or AA are present as such or may form intramolecular disulfide bonds,

   or a salt thereof.

2. A compound of formula I according to claim 1 wherein

   m is 2 to 6,
X is selected from

(i) benzoyl, 1-naphthoyl, 2-naphthoyl; benzoyl substituted with amino; lower alkylamino; amino-lower alkyl; hydroxy; lower alkoxy; amino and hydroxy; amino and lower alkoxy; carboxy; lower-alkoxycarbonyl; cyano; halogen; lower-alkylthio; or lower alkylsulfanyl; and 1- or 2-naphthoyl substituted with amino;

(ii) 1-or 2-naphthalenesulfonfyl which is substituted with amino or mono- or di-lower alkylamino;

(iii) C₃-C₇-cycloalkylcarbonyl which is unsubstituted or substituted by amino;

(iv) pyridylcarbonyl which is unsubstituted or substituted with amino; pyrazinyl which is unsubstituted or substituted with amino; quinolinyl-carbonyl, isoquinolyl, indolylcarbonyl and indolinylicarbonyl, and

(v) quinolinylsulfonfyl;

A is absent or the bivalent radical of an amino acid selected from glycine, alanine, β-alanine, valine, norvaline, leucine, isoleucine, norleucine, α-amino-n-decanoic acid, serine, homoserine, threonine, methionine, cysteine, which is present as such or forms a disulfide bridge with another cysteine B or AA; S-protected cysteine, proline, trans-3- and trans-4-hydroxyproline, phenylalanine, tyrosine, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenylserine, phenylglycine, α-naphthylalanine, cyclohexylalanine, cyclohexylglycine, tryptophan, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aspartic acid, asparagine, aminomalonic acid, aminomalonic acid monoamide, glutamic acid, glutamine, histidine, arginine, lysine, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, δ-hydroxylysine, ornithine, α,γ-diaminobutyric acid and α,β-diaminopropionic acid; it being possible for each of the mentioned amino acids (with the exception of glycine or any other amino acid without asymmetric carbon atom) to be in the D-, L- or (D,L)-form;

B is the bivalent radical of an amino acid as defined above for A;

PTI is a bivalent radical of phosphotyrosine or of a phosphotyrosine mimic in the form of a bivalent radical (which is bound N-terminally via the imino group resulting from the α-amino group and C-terminally via the carbonyl group resulting from its α-carboxy group) of an amino acid selected from phosphonomethyl-phenylalanine, phosphono-(α-fluoro)methyl-
phenylalanine, phosphono-(α,α-difluoro)methyl-phenylalanine, phosphono-(α-hydroxy)-methyl-phenylalanine, O-sulfo-tyrosine, dicarboxymethoxy-phenylalanine, aspartic acid, glutamic acid, phosphoserine and phosphothreonine, each of which is present in the (D,L)-, D- or the L-form;

-(AA)_n- has one of the following meanings:

• a bivalent radical of a tetrapeptide of the formula -(AA¹)-(AA²)-(AA³)-(AA⁴)- wherein -(AA¹)- is selected from -Ile-, -Cys(Acm)-, -Cys- which is present as such or forms a disulfide bond with another -Cys- B, -Ac⁶C-, -Ac⁶C- and -Glu-; -(AA²)- is selected from -Asn-, -Glu- and -Ile-; -(AA³)- is selected from -Gln-, -Cys(Acm)-, -Cys- which is present as such or forms a disulfide bond with another -Cys- B; -Ile- and -Pro-; and -(AA⁴)- is selected from -Cys(Acm)- and -Cys- which is present as such or forms a disulfide bond with another -Cys- B;

• a bivalent radical of a tripeptide of the formula -(AA¹)-(AA²)-(AA³)- wherein -(AA¹)- is selected from -Ile-, -Cys(Acm)-, -Cys- which is present as such or forms a disulfide bond with another -Cys- B and -Glu-; -(AA²)- is selected from -Asn-, -Glu- and -Ile-; and -(AA³)- is selected from -Gln-, -Cys(Acm)-, -Cys- which is present as such or forms a disulfide bond with another -Cys- B; -Ile- and -Pro-; or

• a bivalent radical of a dipeptide of the formula -(AA¹)-(AA²)- wherein -(AA¹)- and -(AA²)- have the meanings given in the last paragraph;

each of the mentioned amino acid radicals being present in the (D,L)-, D- or L-form;

and

Y is a free amino group, a mono- or disubstituted amino group the substituents of which are selected from the group comprising lower alkyl, phenyl-lower alkyl, pyrrolidinyl-lower alkyl, pyridyl-lower alkyl, furyl-lower alkyl, morpholinyl-lower alkyl and indolyl-lower alkyl; or is 1-pyrrolidinyl or 4-morpholinyl,

with the proviso that two or more sulphydryl groups belonging to any amino acid A, B or AA are present as such or may form intramolecular disulfide bonds,

or a salt thereof.
3. A compound of formula I according to claim 1 wherein m is 2, 3 or 4,

X is selected from 4-aminobenzoyl, 3-aminobenzoyl, 2-aminobenzoyl, 3,5-diaminobenzoyl, 2-hydroxybenzoyl, 4-lower alkoxy-benzoyl, and 3-amino-2-naphthoyl;

A is absent or the bivalent amino acid radical of proline which is present in the (D,L)-, D- or L-form;

B is selected from glutamic acid, S-acetamidomethyl-cysteine, cysteine which together with another cysteine AA forms a disulfide bond; glycine, alanine and isoleucine, it being possible for each of the mentioned amino acids (with the exception of glycine or any other amino acid without asymmetric carbon atom) to be in the D-, L- or (D,L)-form;

PTI is a bivalent radical of phosphotyrosine (in the D-, L- or (D,L)-form) or of a phosphotyrosine mimic of the phosphono-(α,α-difluoro)methyl-phenylalanine type, especially 4-phosphono-(α,α-difluoro)methyl-phenylalanine;

-(AA)ₘ⁻ has one of the following meanings:

- a bivalent radical of a tetrapeptide of the formula -(AA¹⁻)(AA²⁻)(AA³⁻)(AA⁴⁻) wherein (AA¹⁻) is selected from -Ile-, -Cys(Acm)-, -Cys- which is present as such or forms a disulfide bond with another -Cys- B and -Glu-; -(AA²⁻) is selected from -Asn-, -Glu- and -Ile-; -(AA³⁻) is selected from -Gln-, -Cys(Acm)- and -Cys-; and -(AA⁴⁻) is selected from -Cys(Acm)- and -Cys- which is present as such or forms a disulfide bond with another -Cys- B;

- a bivalent radical of a tripeptide of the formula -(AA¹⁻)(AA²⁻)(AA³⁻) wherein -(AA¹⁻) is selected from -Ile-, -Cys(Acm)-, -Cys- which is present as such or forms a disulfide bond with another -Cys- B and -Glu-; -(AA²⁻) is selected from -Asn- and -Ile-; and -(AA³⁻) is selected from -Gln-, -Cys(Acm)- and -Cys- which is present as such or forms a disulfide bond with another -Cys- B; or
• a bivalent radical of a dipeptide of the formula -(AA²)-(AA³)- wherein -(AA²)- is -Ile- and -(AA³)- is -Ile- or -Asn-;

each of the mentioned amino acid radicals being present in the the L-form or, in the case of -Cys- or -Cys(Acm)-, in the D- or L-form;

and

Y is amino (-NH₂),

with the proviso that two or more sulfhydryl groups belonging to any amino acid B or AA are present as such or may form intramolecular disulfide bonds,

or a salt thereof.

4. A compound of formula I according to claim 1 being selected from the following compounds:

Dansyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂ (TFA salt)
(SEQ ID NO: 2);

2-aminobenzoyl-Pro-Glu-Tyr(PO₃H₂)-Ile-Asn-NH₂
(SEQ ID NO: 3);

1-aminocyclohexyl-carbonyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 4);

2-amino-nicotinoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 8);

3,5-diaminobenzoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 9);

2-aminobenzoyl-Gln-Tyr(PO₃H₂)-Glu-Glu-Ile-NH₂
(SEQ ID NO: 10);

3-amino-2-naphtoyl-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 12);

2-aminobenzoyl-Cys(Acm)-Tyr(PO₃H₂)-Ile-Asn-Gln-Cys(Acm)-NH₂
(SEQ ID NO: 13);

2-aminobenzoyl-Cys(Acm)-Tyr(PO₃H₂)-Ile-Asn-D-Cys(Acm)-NH₂
(SEQ ID NO: 15);
2-aminobenzoxyI-Asp-Tyr(PO₃H₂)-Ile-Ile-NH₂
(SEQ ID NO: 16);
2-aminobenzoxyI-Asp-Tyr(PO₃H₂)-Ile-Ile-Pro-NH₂
(SEQ ID NO: 17);
2-aminobenzoxyI-βAla-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 19);
2-aminobenzoxyI-Leu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 21);
2-aminobenzoxyI-Val-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 22);
4-aminobenzoxyI-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 24);
quinoIine-3-yIcarbonyI-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 26);
quinoIine-2-yIcarbonyI-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 27);
quinoIine-8-ylsulfonIyI-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 30);
indole-2-yIcarbonyI-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 32);
3-aminopyrazine-2-yIcarbonyI-Glu-Tyr(PO₃H₂)-Ile-Asn-Gln-NH₂
(SEQ ID NO: 34);
3-aminobenzoxyI-Glu-F₂Pmp-Ile-Asn-Gln-NH₂
(SEQ ID NO: 36);
2-aminobenzoxyI-Cys-Tyr(PO₃H₂)-Ile-Asn-Cys-NH₂
    |                     |  
    S----------------S
(SEQ ID NO: 37);
2-aminobenzoxyI-Cys-Tyr(PO₃H₂)-Cys-Asn-Gln-NH₂
    |                     |  
    S----------------S
(SEQ ID NO: 39);
2-aminobenzoxyI-Cys-Tyr(PO₃H₂)-Ile-Asn-D-Cys-NH₂
or a pharmaceutically acceptable salt thereof if a salt-forming group is present.

5. A compound of formula I according to claim 1 being selected from the following compounds:

2-Aminobenzoyl-Glu-Tyr(PO$_3$H$_2$)-Ile-Asn-Gln-NH$_2$
(SEQ ID NO: 40); and

2-hydroxy-benzoyl-Glu-Tyr(PO$_3$H$_2$)-Ile-Asn-Gln-NH$_2$
(SEQ ID NO: 41),

indoline-2-ylcarbonyl-Glu-Tyr(PO$_3$H$_2$)-Ile-Asn-Gln-NH$_2$
(SEQ ID NO: 31);
(SEQ ID NO: 42); and
2-Aminobenzoyl-Glu-Tyr(PO₃H₂)-Acetyl-Asn-NH₂
(SEQ ID NO: 43);

or a pharmaceutically acceptable salt thereof if a salt-forming group is present.

6. 2-Aminobenzoyl-Phe-Tyr(PO₃H₂)-Ile-Asn-NH₂ (SEQ ID NO: 46) of formula I according to claim 1, or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical preparation comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier material.

8. A compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 for use in a method for the therapeutic or prophylactic treatment of the warm-blooded animal or human body.

9. The use of a compound of formula I, or a salt thereof, according to any one of claims 1 to 6 for the preparation of a pharmaceutical composition for the treatment of a disease that responds to inhibition of the interaction of a protein comprising an SH2 domain with a protein tyrosine kinase.

10. A process for the preparation of a compound of formula I according to claim 1, comprising reacting a fragment of a compound of formula I, which has a free carboxy group or a reactive derivative thereof, or, in the case of the introduction of X, a free carboxy or sulfo group, or a reactive derivative thereof, with a complementary fragment that has an amino group with at least one free hydrogen atom, or with a reactive derivative thereof, with formation of an amide bond; in the mentioned fragments free functional groups with the exception of those that participate in the reaction if required being present in protected form; and removing any protecting groups present;

and, if desired, transforming a compound of formula I into a different compound of formula I; transforming a salt of an obtainable compound of formula I into the free compound or a
different salt or an obtainable free compound of formula I into a salt; and/or separating obtainable mixtures of isomers of compounds of formula I into the individual isomers.
### INTERNATIONAL SEARCH REPORT

**International Application:** No

**PCT/EP 96/03479**

### A. CLASSIFICATION OF SUBJECT MATTER

**IPC 6**
- C07K7/02
- C07K7/06
- A61K38/08

This classification is based on the International Patent Classification (IPC) or both national classification and IPC.

### B. FIELDS SEARCHED

**Minimum documentation searched**
- IPC 6
- C07K
- A61K

Documentation searched other than minimum documentation is included in the fields searched.

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim: No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 94 07913 A (WARNER LAMBERT CO) 14 April 1994 see page 14; table 1 see claims; examples 40,41</td>
<td>1,2,7-9</td>
</tr>
<tr>
<td>X</td>
<td>PROTEIN ENG. (1995), 8(6), 527-33 CODEN: PRENEG; ISSN: 0269-2139, June 1995, XP002023104 ZVELEBLIL, MARKETA J. J. M. ET AL: &quot;Prediction and analysis of SH2 domain-phosphopeptide interactions&quot; see page 533, right-hand column, paragraph 2; table 1</td>
<td>1,2,7-9</td>
</tr>
</tbody>
</table>

**Further documents are listed in the continuation of box C.**

**Patent family members are listed in annex.**

- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document published on or after the international filing date
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referred to in an oral disclosure, use, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed
- **T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- **&** document member of the same patent family

### Date of the actual completion of the international search

20 January 1997

### Date of mailing of the international search report

03.02.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo.nl, Fax (+31-70) 340-3016

Authorized officer

Fuhr, C
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>CURR. BIOL. (1995), 5(4), 404-12 CODEN: CUBLE2;ISSN: 0960-9822, 1 April 1995, XP000615948 VANDER GEER, PETER ET AL: &quot;A conserved amino-terminal Shc domain binds to phosphotyrosine motifs in activated receptors and phosphopeptides&quot; see table 1</td>
<td>1,2</td>
</tr>
<tr>
<td>P,X</td>
<td>J. BIOL. CHEM. (1995), 270(45), 26738-41 CODEN: JBCHA3;ISSN: 0021-9258, 10 November 1995, XP002023105 COWBURN, DAVID ET AL: &quot;Enhanced affinities and specificities of consolidated ligands for the Src homology (SH) 3 and SH2 domains of Abelson protein-tyrosine kinase&quot; see page 26740, right-hand column, paragraph 2 - paragraph 3; table 1</td>
<td>1,2,7-9</td>
</tr>
<tr>
<td>P,X</td>
<td>EUR. J. IMMUNOL. (1995), 25(10), 2978-84 CODEN: EJIMAF;ISSN: 0014-2980, October 1995, XP000615951 CHALUPNY, N. JAN ET AL: &quot;Specific binding of Fyn and phosphatidylinositol 3-kinase to the B cell surface glycoprotein CD19 through their src homology 2 domains&quot; see page 2982, left-hand column, paragraph 2 - page 2983, left-hand column, paragraph 1; table 1</td>
<td>1,2,7-9</td>
</tr>
<tr>
<td>X</td>
<td>BIOORG. MED. CHEM. LETT. (1995), 5(4), 353-6 CODEN: BCMLE8;ISSN: 0960-894X, 1995, XP000615949 BOBKOV, MARK ET AL: &quot;CD45 protein tyrosine phosphatase: determination of minimal peptide length for substrate recognition and synthesis of some tyrosine-based electrophiles as potential active-site directed irreversible inhibitors&quot; see table 1</td>
<td>1,2</td>
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<td>A</td>
<td>WO 94 08600 A (JOSLIN DIABETES CENTER INC) 28 April 1994 see claims; examples</td>
<td>1,7-9</td>
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</tbody>
</table>
Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:

2. X Claims Nos.: 1-3 and 7-10  
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

   * see continuation-sheet PCT/ISA/210 *

3. □ Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

□ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.
Claims searched incompletely: 1-3 and 7-10:

In view of the extremely large number of compounds falling under these claims, and of the absence of any technical support for these compounds in the description, the International Searching Authority considers that it is not economically reasonable to draw a search report covering the entire subject matter characterized above.

The search has therefore been limited to the real examples given in the description and closely related ones and includes compounds having the alleged activities.
### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
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