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Detectable somatostatin analogues containing a chelating group

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(58) Field of search

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CASE 100-7382/W

DETECTABLE SOMATOSTATIN DERIVATIVES CONTAINING A CHELATING GROUP

The present invention relates to polypeptides, process for their production, pharmaceutical preparations containing them and their use as a pharmaceutical, e.g. for treatment of somatostatin receptor positive tumors or as in vivo diagnostic imaging agents.

In the last few years a high incidence of somatostatin receptors has been demonstrated in a variety of human tumors, e.g. pituitary tumors, central nervous system tumors, breast tumors, gastro-enteropancreatic tumors and their metastases. Some of them are small or slow-growing tumors which are difficult to precisely localize by conventional diagnosis methods.

In vitro visualization of somatostatin receptors has been performed through autoradiography of tumoral tissues using radioiodinated somatostatin or somatostatin analogues, e.g.

[¹²⁵I-Tyr¹¹] somatostatin-14 (Taylor, J.E. et al., Life Science (1988) 43: 421), or [¹²⁵I-Tyr³] SMS 201-995 also called [¹²⁵I] 204-090 (Reubi, J.C. et al., Brain Res. (1987) 406: 891; Reubi, J.C. et al., J. Clin. Endocr. Metab. (1987) 65: 1127; Reubi, J.C. et al., Cancer Res. (1987) 47: 551; Reubi, J.C. et al., Cancer Res. (1987) 47: 5758).

New somatostatin peptides useful in therapeutic and which can be labelled for in vivo diagnostic and therapeutic applications have now been found.

According to the invention, there is provided a somatostatin peptide bearing at least one chelating group for a detectable element, this chelating group being linked to an amino group of said peptide, this amino group having no significant binding affinity for somatostatin receptors, the thus modified somatostatin peptide having binding affinity for somatostatin receptors, and the chelating group being other than a sugar residue.

These compounds are referred to thereafter as LIGANDS OF THE INVENTION. They possess one chelating group capable of reacting with a detectable element, e.g. a radionuclide, a radioopaque element or a paramagnetic ion, to form a complex and further are capable of binding to somatostatin receptors, e.g. expressed or overexpressed by tumors or metastases.

The chelating group is linked by a covalent bond to the amino group of the peptide.

The chelating group is preferably attached to the terminal N-amino group of the somatostatin peptide.

According to the invention, the chelating group may be attached either directly or indirectly, e.g. by means of a spacer group, to the amino group of the somatostatin peptide.

One group of LIGANDS is that wherein the chelating group is attached directly to the amino group of the somatostatin peptide.

Another group of LIGANDS is that wherein the chelating group is attached indirectly by a bridging or a spacer group to the amino group of the somatostatin peptide.

Preferably the chelating group is attached by an amide bond to the peptide.

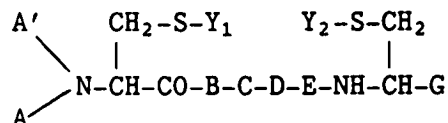
The term somatostatin peptides includes the naturally occurring somatostatin (tetradecapeptide) and its analogues or derivatives.

By derivatives or analogues as used herein is meant any straight-chain or cyclic polypeptide derived from that of the naturally occurring tetradecapeptide somatostatin wherein one or more amino acid units have been omitted and/or replaced by one or more other amino acid radical(s) and/or wherein one or more functional groups have been replaced by one or more other functional groups and/or one or more groups have been replaced by one or several other isosteric groups. The term covers all modified derivatives of a biologically active peptide which exhibit a qualitatively similar effect to that of the unmodified somatostatin peptide, e.g. they bind to somatostatin receptors and decrease hormone secretion.

Cyclic, bridge cyclic and straight-chain somatostatin analogues are known compounds. Such compounds and their preparation are described e.g. in European Patent Specifications EP-A-1295; 29,579; 215,171; 203,031; 214,872; 298,732; 277,419.

Preferred LIGANDS OF THE INVENTION are those derived from the following somatostatin analogues:

A. Analogues of formula I



I

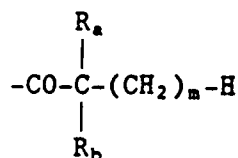
wherein

A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula $RCO-$, whereby

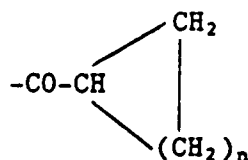
- i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl, or
- ii) $RCO-$ is
 - a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy;
 - b) the residue of a natural or synthetic α -amino acid other than defined under a) above or of a corresponding D-amino acid, or
 - c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

the α -amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- C_{1-12} alkylated or substituted by C_{1-8} alkanoyl,

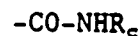
A' is hydrogen, C_{1-12} alkyl or C_{7-10} phenylalkyl,
 Y_1 and Y_2 represent together a direct bond or
each of Y_1 and Y_2 is independently hydrogen or a radical of formulae (1) to (5)



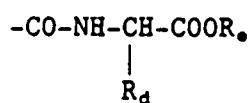
(1)



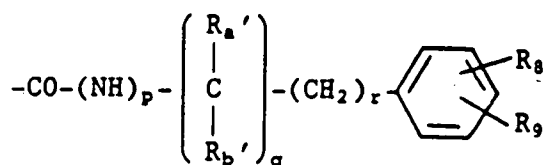
(2)



(3)



(4)

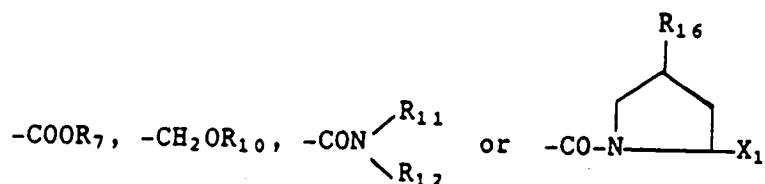


(5)

wherein

- R_a is methyl or ethyl
- R_b is hydrogen, methyl or ethyl
- m is a whole number from 1 to 4
- n is a whole number from 1 to 5
- R_c is (C_{1-6}) alkyl
- R_d represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen)
- R_e is (C_{1-5}) alkyl
- $R_{a'}$ and $R_{b'}$ are independently hydrogen, methyl or ethyl,
- R_8 and R_9 are independently hydrogen, halogen, (C_{1-3}) alkyl or (C_{1-3}) alkoxy,
- p is 0 or 1,
- q is 0 or 1, and
- r is 0, 1 or 2,
- B is -Phe- optionally ring-substituted by halogen, NO_2 , NH_2 , OH , C_{1-3} alkyl and /or C_{1-3} alkoxy (including pentafluoroalanine), or β -naphthyl-Ala

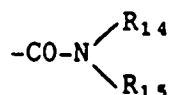
- C is (L)-Trp- or (D)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy,
- D is Lys, Lys in which the side chain contains O or S in β -position, γ F-Lys or δ F-Lys, optionally α -N-methylated, or a 4-aminocyclohexylAla or 4-aminocyclohexylGly residue
- E is Thr, Ser, Val, Phe, Ile or an aminoisobutyric or aminobutyric acid residue
- G is a group of formula



wherein

- R_7 is hydrogen or C_{1-3} alkyl,
- R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
- R_{11} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenylalkyl,
- R_{12} is hydrogen, C_{1-3} alkyl or a group of formula $-\text{CH}(\text{R}_{13})-\text{X}_1$,
- R_{13} is CH_2OH , $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, or $-\text{CH}(\text{CH}_3)\text{OH}$ or represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen) and

X_1 is a group of formula $-COOR_7$, $-CH_2OR_{10}$ or



wherein

R_7 and R_{10} have the meanings given above,

R_{14} is hydrogen or C_{1-3} alkyl and

R_{15} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenyl-alkyl, and

R_{16} is hydrogen or hydroxy,

with the proviso that

when R_{12} is $-CH(R_{13})-X_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2-and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)- configuration.

The significances of A and A' in formula I are preferably selected so that the compound contains a terminal $-NH-$ group capable of being linked to a chelating agent.

In the compounds of formula I, the following significances are preferred either individually or in any combination or sub-combination:

1. A is C_{7-10} phenylalkyl, especially phenethyl, or a group of formula RCO. Preferably A is a group of formula RCO.

1.1. Preferably R is C_{1-11} alkyl or C_{7-10} phenylalkyl, especially C_{7-10} phenylalkyl, more especially phenethyl, or RCO has the meanings a), b) or c).

1.2. When RCO has the meanings a), b) or c), the α -amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) is preferably non-alkylated or mono-C₁₋₁₂ alkylated, especially -C₁₋₈ alkylated, more especially -methylated. Most preferably the N-terminal is non-alkylated.

1.3. When RCO has the meaning a) this is preferably a') an L- or D-phenylalanine or -tyrosine residue optionally mono-N-C₁₋₁₂ alkylated. More preferably a') is an L- or D-phenylalanine residue.

1.4. When RCO has the meaning b) or c) the defined residue is preferably lipophilic. Preferred residues b) are thus b') α -amino acid residues having a hydrocarbon side chain, e.g. alkyl with 3, preferably 4, or more C atoms, e.g. up to 7 C-atoms, naphthyl-methyl or heteroaryl, e.g. 3-(2- or 1-naphthyl)-alanine, pyridyl-methyl or tryptophane residue, said residues having the L- or D-configuration, and preferred residues c) are dipeptide residues in which the individual amino acid residues are the same or different and are selected from those defined under a') and b') above.

1.5. Most preferably RCO has the meaning a) especially the meaning a').

2. B is B', where B' is Phe or Tyr.

3. C is C', where C' is (D)Trp.

4. D is D', where D' is Lys or MeLys, especially Lys.

5. E is E', where E' is Val or Thr, especially Thr.

6. G is G', where G' is a group of formula $-\text{CO}-\text{N} \begin{array}{l} \nearrow \text{R}_{11} \\ \searrow \text{R}_{12} \end{array}$,

especially a group of formula $-\text{CO}-\text{N} \begin{array}{l} \nearrow \text{R}_{11} \\ \searrow \text{CH}(\text{R}_{13})-\text{X}_1 \end{array}$

(in which case $\text{R}_{11}=\text{H}$ or CH_3). In the latter case the moiety $-\text{CH}(\text{R}_{13})-\text{X}_1$ preferably has the L-configuration.

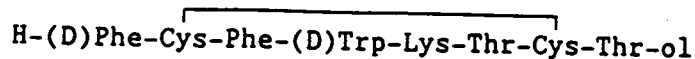
6.1. R_{11} is preferably hydrogen.

6.2. As the substituent attached to the α -carbon atom of a natural amino acid (i.e. of formula $\text{H}_2\text{N}-\text{CH}(\text{R}_{13})-\text{COOH}$), R_{13} is preferably $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_3)-\text{OH}$, isobutyl or butyl, or R_{13} is $-(\text{CH}_2)_2-\text{OH}$ or $-(\text{CH}_2)_3-\text{OH}$. It is especially $-\text{CH}_2\text{OH}$ or $-\text{CH}(\text{CH}_3)\text{OH}$.

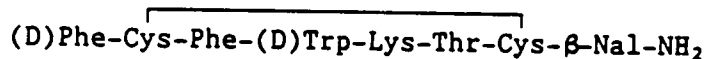
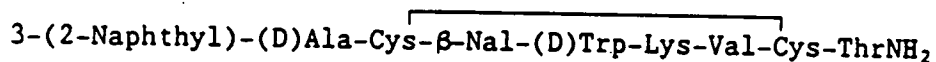
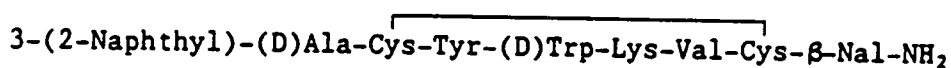
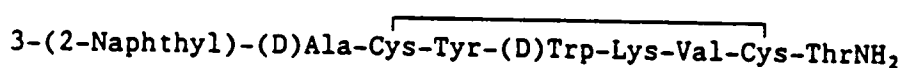
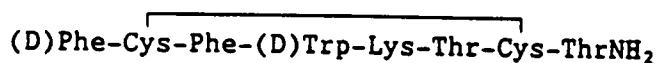
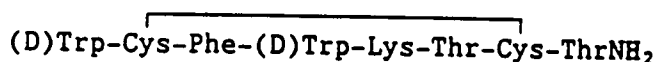
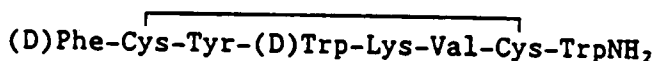
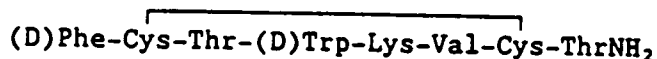
6.3. X_1 is preferably a group of formula $-\text{CO}-\text{N} \begin{array}{l} \nearrow \text{R}_{14} \\ \searrow \text{R}_{15} \end{array}$

or $-\text{CH}_2-\text{OR}_{10}$, especially of formula $-\text{CH}_2-\text{OR}_{10}$ and R_{10} is preferably hydrogen or has the meaning given under 7 below. Most preferably R_{10} is hydrogen.

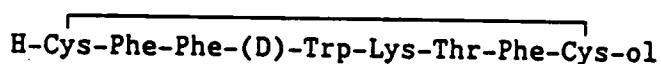
The following individual compounds are illustrative of compounds of formula I:



also known as octreotide

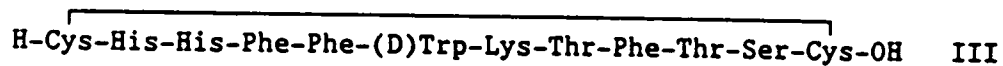


B. Analogues of formula II



II

[see Vale et al., Metabolism, 27, Supp. 1, 139, (1978)]

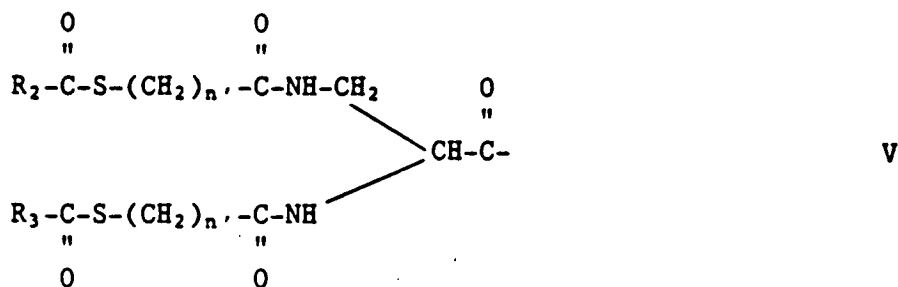


III

(see EP-A-200,188)

The contents of all the above publications including the specific compounds are specifically incorporated herein by reference.

H-(D)Phe-Cys-Phe-(D)Trp-Lys-Thr-Cys-Thr-ol.

$$\begin{array}{c} \text{O} \qquad \qquad \text{O} \qquad \qquad \text{O} \\ \parallel \qquad \qquad \parallel \qquad \qquad \parallel \\ \text{R}_1-\text{C}-\text{S}-(\text{CH}_2)_n-\text{C}-(\text{TT})_4-\text{C}- \end{array} \quad \text{IV}$$


wherein

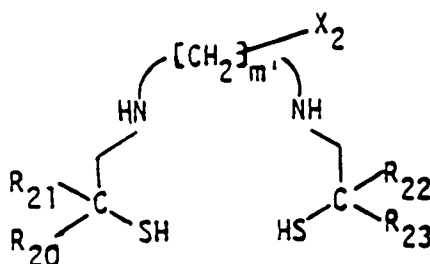
each of R_1 , R_2 and R_3 independently is C_{1-6} alkyl, C_{6-8} aryl or C_{7-9} arylalkyl, each optionally substituted by OH, C_{1-4} alkoxy, COOH or SO_3H ,

n' is 1 or 2,

i is an integer from 2 to 6, and

TT are independently α or β amino acids linked to each other by amide bonds,

groups derived from bis-aminothiol derivatives, e.g. compounds of formula VI



VI

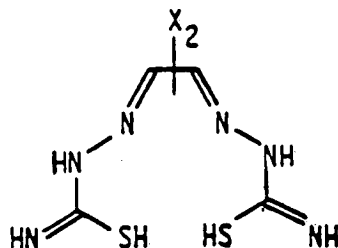
wherein

each of R_{20} , R_{21} , R_{22} and R_{23} independently is hydrogen or C_{1-4} alkyl,

X_2 is a group capable of reacting with the N-amino group of the peptide, and

m' is 2 or 3,

groups derived from dithiasemicarbazone derivatives, e.g. compounds of formula VII

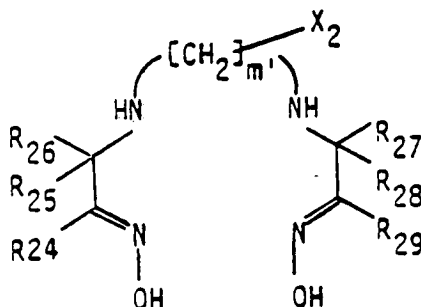


VII

wherein

X_2 is as defined above,

groups derived from propylene amine oxime derivatives, e.g. compounds of formula VIII



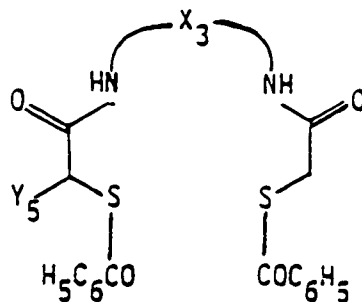
VIII

wherein

each of R_{24} , R_{25} , R_{26} , R_{27} , R_{28} and R_{29} independently are hydrogen or C_{1-4} alkyl, and

X_2 and m' are as defined above,

groups derived from diamide dimercaptides, e.g. compounds of formula IX



IX

wherein

X_3 is a divalent radical optionally substituted and bearing a group capable of reacting with the N-amino group of the peptide, e.g. C_{1-4} alkylene or phenylene bearing a group X_2 , and

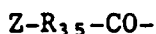
Y_5 is hydrogen or CO_2R_{30} , wherein R_{30} is C_{1-4} alkyl,

or groups derived from porphyrins, e.g. N-benzyl-5,10,15,20-tetrakis-(4-carboxyphenyl)porphine or TPP bearing a group X_2 as defined above.

Aryl is preferably phenyl. Arylalkyl is preferably benzyl.

Examples of X_2 include radicals of formula $-(X_4)_n--X_5$, wherein X_4 is C_{1-6} alkylene; or C_{1-6} alkylene optionally attached to the carbon atom by an oxygen atom or $-NH-$, n'' is 0 or 1 and X_5 is $-NCS$, a carboxy group or a functional derivative thereof, e.g. acid halide, anhydride or hydrazide. It is understood that X_2 is attached to one of the carbon atom of $-[CH_2]_n-$ or $=CH-CH=$ in replacement of an hydrogen atom.

The chelating group may be attached either directly or indirectly to the N-amino group of the somatostatin peptide. When it is attached indirectly, it is preferably linked through a bridging or spacer group, for example a group of formula (α 1)



(α_1)

R_{35} is C_{1-11} alkylene, C_{2-11} alkenylene or $-CH(R')$ - wherein R' is the residue attached in α to a natural or synthetic α -amino acid, e.g. hydrogen, C_{1-11} alkyl, benzyl, optionally substituted benzyl, naphthyl-methyl, pyridyl-methyl,

Z is a functional moiety capable of covalently reacting with the chelating agent.

Z may be for example a group which can form an ether, ester or amide bonding with the chelating group. Z is preferably amino.

The chelating groups, when comprising carboxy, $-SO_3H$ and/or amino groups may exist in free form or in salt form.

Preferred chelating groups are those derived from polyamino-poly-carboxylic groups, e.g. those derived from EDTA, DTPA, DOTA, TETA or substituted EDTA or DTPA. Chelating groups derived from DTPA are most preferred.

In the LIGANDS OF THE INVENTION the chelating group, when poly-functional, may be linked either to a single somatostatin peptide molecule or to more than one somatostatin peptide molecules e.g. to two somatostatin peptide molecules.

The LIGANDS OF THE INVENTION may exist e.g. in free or salt form. Salts include acid addition salts with e.g. organic acids, polymeric acids or inorganic acids, for example hydrochlorides and acetates, and salt forms obtainable with the carboxylic or sulphonic acid groups present in the chelating group, e.g. alkali metal salts such as sodium or potassium, or substituted or unsubstituted ammonium salts.

The present invention also includes a process for the production of the LIGANDS OF THE INVENTION. They may be produced by analogy to known methods.

The LIGANDS OF THE INVENTION may be produced for example as follows:

- a) removing at least one protecting group which is present in a somatostatin peptide bearing a chelating group, or
- b) linking together by an amide bond two peptide fragments each of them containing at least one amino acid or amino alcohol in protected or unprotected form and one of them containing the chelating group, wherein the amide bond is in such a way that the desired amino acid sequence is obtained, and stage a) of the process is then optionally effected, or
- c) linking together a chelating agent and the desired somatostatin peptide in protected or unprotected form in such a way that the chelating group is fixed on the desired N-amino group of the peptide, and stage a) is then optionally effected or,
- d) removing a functional group of an unprotected or a protected peptide bearing a chelating group or converting it into another functional group so that another unprotected or protected peptide bearing a chelating group is obtained and in the latter case stage a) of the process is effected, or
- e) oxidising a somatostatin peptide modified by a chelating group in which the mercapto groups of Cys radicals exist in free form so as to produce an analogue in which two Cys radicals are joined by an S-S-bridge

and recovering the LIGAND thus obtained in free form or in salt form.

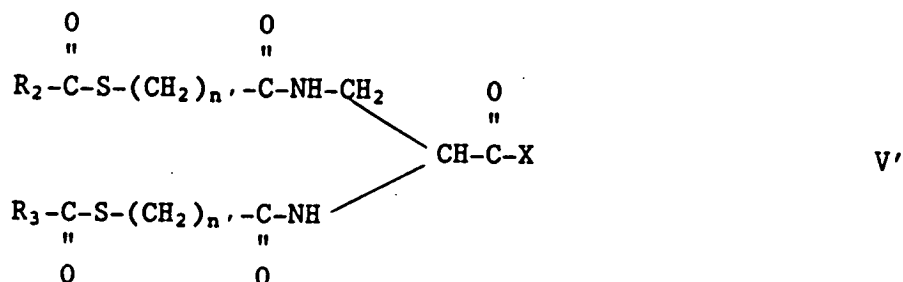
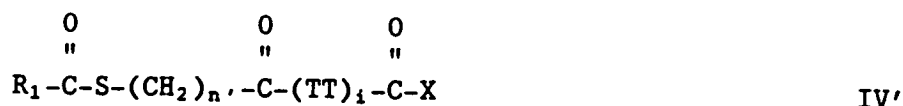
The above reactions may be effected in analogy with known methods, e.g. as described in the following examples, in particular processes a) and c). When the chelating group is attached by an amide bond, this may be carried out analogously to the methods used for amide formation. Where desired, in these reactions, protecting groups which are suitable for use in peptides or for the desired chelating groups may be used for functional groups which do not participate in the reaction. The term protecting group may also include a polymer resin having functional groups.

When it is desired to attach the chelating group to the terminal N-amino group of a peptide or peptide fragment used as starting material, and which comprises one or more side chain amino groups, these side chain amino groups are conveniently protected with a protecting group, e.g. as used in peptide chemistry.

When it is desired to attach the chelating group to a side chain amino group of a peptide or peptide fragment used as starting material, and the peptide comprises a free terminal N-amino group, the latter is preferably protected with a protecting group.

The peptide fragment bearing the chelating group and used in stage b) may be prepared by reacting the peptide fragment comprising at least one amino acid or amino alcohol in protected or unprotected form with the chelating agent. The reaction may be performed in analogy with stage c).

The chelating groups of formula IV or V may be linked to a peptide by reacting a chelating agent of formula IV' or V'



wherein X is an activating group capable of forming an amide bond with the N-amino group of the peptide. The reaction may be performed as disclosed in EP 247,866 A1.

The chelating agent used in process step c) may be known or prepared in analogy with known procedures. The compound used is such that it allows the introduction of the desired chelating group on the somatostatin peptide, e.g. a polyaminopolycarboxylic acid as disclosed, a salt or anhydride thereof.

In the above process, when in the amino-acids, peptide fragments or peptides used as starting materials, the chelating group is attached through a bridging or spacer group to the peptide, e.g. a radical of formula (α_1) as defined above, such amino-acids, peptide fragments or peptides may be prepared by reacting in conventional manner the corresponding amino-acids or peptides free of bridging or spacer group with a corresponding bridging- or spacer-yielding compound, for example an acid or reactive acid derivative comprising the bridging or spacer group, e.g. an acid of formula $Z-R_{3,5}-COOH$ or a reactive acid derivative thereof such as an active ester. Examples of active ester groups or carboxy activating groups are e.g. 4-nitrophenyl, pentachlorophenyl, pentafluorophenyl, succinimidyl or 1-hydroxy-benzotriazolyl.

Alternatively the chelating agent may first be reacted with a bridging or spacer group-yielding compound, in order to bear the bridging or spacer group and then be reacted in conventional manner with the peptide, peptide fragment or amino-acid.

The LIGANDS OF THE INVENTION may be purified in conventional manner, e.g. by chromatography. Preferably the LIGANDS OF THE INVENTION contain less than 5% by weight of peptides free of chelating groups.

The LIGANDS OF THE INVENTION in free form or in the form of pharmaceutically acceptable salts are valuable compounds. According to a further embodiment, the LIGANDS OF THE INVENTION can be complexed with a detectable element.

Accordingly, the present invention also provides the LIGANDS OF THE INVENTION as defined above which are complexed with a detectable element (hereinafter referred to as CHELATES OF THE INVENTION), in free form or in salt form, their preparation and their use for in vivo diagnostic and therapeutic treatment.

By detectable element is meant any element, preferably a metal ion which exhibits a property detectable in therapeutic or in vivo diagnostic techniques, e.g. a metal ion which emits a detectable radiation or a metal ion which is capable of influencing NMR relaxation properties.

Suitable detectable metal ions include for example heavy elements or rare earth ions, e.g. as used in CAT scanning (Computer axial tomography), paramagnetic ions, e.g. Gd^{3+} , Fe^{3+} , Mn^{2+} and Cr^{2+} , fluorescent metal ions, e.g. Eu^{3+} , and radionuclides, e.g. γ -emitting radionuclides, β -emitting radionuclides, α -emitting radionuclides, positron-emitting radionuclides e.g. ^{68}Ga .

Suitable γ -emitting radionuclides include those which are useful in diagnostic techniques. The γ -emitting radionuclides advantageously have a half-life of from 1 hour to 40 days, preferably from 5 hours to 4 days, more preferably from 12 hours to 3 days. Examples are radionuclides derived from Gallium, Indium, Technetium, Ytterbium, Rhenium and Thallium e.g. ^{67}Ga , ^{111}In , $^{99\text{m}}\text{Tc}$, ^{169}Yb and ^{186}Re . Preferably the γ -radionuclide is selected depending on the metabolism of the LIGAND OF THE INVENTION or somatostatin peptide used. More preferably the LIGAND OF THE INVENTION is chelated with a γ -radionuclide having a longer half-life than the half-life of the somatostatin peptide on the tumor.

Further radionuclides suitable for use in imaging are positron-emitting radionuclides, e.g. as mentioned above.

Suitable β -emitting radionuclides include those which are useful in therapeutic applications, for example ^{90}Y , $^{67}\text{-Cu}$, ^{186}Re , ^{188}Re , ^{169}Er , ^{121}Sn , ^{127}Te , ^{143}Pr , ^{198}Au , ^{109}Pd , ^{165}Dy , ^{32}P , ^{142}Pr . The β -radionuclide advantageously have a half-life of from 2.3 hrs to 14.3 d, preferably from 2.3 to 100 hrs. Preferably the β -emitting radionuclide is selected in order to have a longer half-life than the half-life of the somatostatin peptide on the tumor.

Suitable α -emitting radionuclides are those which are used in therapeutic treatments, e.g. ^{211}At , ^{212}Bi .

The CHELATES OF THE INVENTION may be prepared by reacting the LIGAND with a corresponding detectable element yielding compound, e.g. a metal salt, preferably a water-soluble salt. The reaction may be carried out by analogy with known methods, e.g. as disclo-

sed in Perrin, Organic Ligand, Chemical Data Series 22. NY Pergamon Press (1982); in Krejcarit and Tucker, Biophys. Biochem. Res. Com. 77: 581 (1977) and in Wagner and Welch, J. Nucl. Med. 20: 428 (1979).

Preferably the complexing of the LIGAND is effected at a pH at which the LIGAND OF THE INVENTION is physiologically stable.

Alternatively the detectable element may also be provided to the solution as a complex with an intermediate chelating agent, e.g. a chelating agent which forms a chelate complex that renders the element soluble at the physiological pH of the LIGAND but is less thermodynamically stable than the CHELATE. Example of such an intermediate chelating agent is 4,5-dihydroxy-1,3-benzene-disulfonic acid (Tiron). In such a process, the detectable element exchanges the ligand.

The CHELATES OF THE INVENTION may also be produced by linking together a chelating agent complexed with the detectable element, and a somatostatin peptide in protected or unprotected form and if desired removing at least one protecting group which is present. The same reaction may be performed with a chelating agent complexed with a non detectable metal ion and then in the resulting complexed peptide the metal ion may be replaced by the desired detectable element.

The CHELATES OF THE INVENTION may also be produced by linking together a chelating agent complexed with the detectable element, and a somatostatin peptide fragment comprising at least one amino acid in protected or unprotected form and then continuing the peptide synthesis step by step until the final peptide sequence is obtained and if desired removing at least one protecting group which is present. Instead of the detectable element the chelating agent may be complexed with a non detectable metal and this metal

may then be replaced by the detectable element in the resulting complexed somatostatin peptide.

Where the chelating group is attached through a bridging or spacer group to the somatostatin peptide, e.g. through a radical of formula (α_1) as defined above, either the somatostatin peptide or peptide fragment or the chelating agent may bear said bridging or spacer group.

The above mentioned reactions may be effected in analogy to known methods. Depending on the chelating group present, the labeling efficiency may approach 100% so that purification is not required. Radionuclides such as for example Technetium-99m may be used in oxidized form, e.g. Tc-99m pertechnetate, which may be complexed under reducing conditions.

The above mentioned reactions are conveniently effected under conditions avoiding trace metal contamination. Preferably distilled de-ionized water, ultrapure reagents, chelation-grade radioactivity etc..are used to reduce the effects of trace metal.

The CHELATES OF THE INVENTION may exist e.g. in free or salt form. Salts include acid addition salts with e.g. organic acids, polymeric acids or inorganic acids, for example hydrochlorides and acetates, and salt forms obtainable with the carboxylic acid groups present in the molecule which do not participate to the chelate formation, e.g. alkali metal salts such as sodium or potassium, or substituted or unsubstituted ammonium salts.

The CHELATES OF THE INVENTION and their pharmaceutical acceptable salts exhibit pharmaceutical activity and are therefore useful either as an imaging agent, e.g. visualisation of somatostatin receptor positive tumors and metastases when complexed with a paramagnetic, a γ -emitting metal ion or a positron-emitting

radionuclide, or as a radiopharmaceutical for the treatment in vivo of somatostatin receptor positive tumors and metastases when complexed with a α - or β -radionuclide, as indicated by standard tests.

In particular, the CHELATES OF THE INVENTION possess affinity for somatostatin receptors expressed or overexpressed by tumors and metastases, as indicated in standard in vitro binding assays.

A somatostatin receptor positive tumor originating from the human gastro intestinal tract is removed from a patient and immediately put on ice and within a maximal delay of 30 min frozen at - 80 ° C. For further autoradiography this frozen material is cut on a cryostat (Leitz 1720) in 10 μ m sections, mounted on pre-cleaned microscope slides and stored at - 20 ° C for at least 3 days to improve adhesion of the tissue to the slide. The sections are preincubated in Tris-HCl buffer (50 mM, pH 7.4), containing CaCl_2 (2mM) and KCl (5mM), for 10 min at ambient temperature and then washed twice for 2 min in the same buffer without additional salts added. The sections are then incubated with a CHELATE OF THE INVENTION for 2 hours at ambient temperature in Tris-HCl buffer (170 mM, pH 7.4), containing bovine serum albumin (10 g/l), bacitracin (40 mg/l) and MgCl_2 (5 mM) to inhibit endogenous proteases. Non-specific binding is determined by adding the corresponding non-labelled, non-modified somatostatin peptide at a concentration of 1 μ M. Incubated sections are washed twice for 5 min in cold incubation buffer containing 0.25 g/l BSA. After a brief dip in distilled water to remove excess salts, the sections are dried quickly and apposed to [^3H]-LKB films. After a time exposure of about 1 week in X-ray cassettes, it is observed that the CHELATES OF THE INVENTION, e.g. a radionuclide CHELATE, give very good results in labeling the tumoral tissue without labeling the surrounding healthy tissue when added at a concentration of about 10^{-10} to 10^{-3} M.

The affinity of the CHELATES OF THE INVENTION for somatostatin receptors can also be shown by in vivo testing.

Rats bearing transplantable exocrine pancreatic somatostatin receptor positive tumors are treated with an intravenous injection of a CHELATE OF THE INVENTION. Injection site is the penis vein. Immediately after administration, the animals are positioned on the collimator of a gamma-camera and the distribution of radioactivity is monitored at various time intervals.

Biodistribution of radioactivity may also be determined through serial sacrifice of a number of such treated rats and determination of the organ radioactivity.

After administration of a CHELATE OF THE INVENTION, e.g. a radionuclide CHELATE, for example a γ -emitting CHELATE, at a dosage of from 1 to 5 $\mu\text{g/kg}$ of LIGAND labeled with 0.1 to 2 mCi radionuclide the tumor site becomes detectable together with the organs where excretion essentially takes place.

CHELATES OF THE INVENTION for use in in vivo detection are the CHELATES which are complexed with a γ -emitting radionuclide, a positron-emitting radionuclide or a paramagnetic metal ion, e.g. as indicated above.

The CHELATES OF THE INVENTION for use as an imaging agent in method (1) may be administered parenterally, preferably intravenously, e.g. in the form of injectable solutions or suspensions, preferably in a single injection. The appropriate dosage will of course vary depending upon, for example, the LIGAND and the type of detectable element used, e.g. the radionuclide. A suitable dose to be injected is in the range to enable imaging by photoscanning procedures known in the art. When a radiolabeled CHELATE OF THE INVENTION is used, it may advantageously be

administered in a dose having a radioactivity of from 0.1 to 50 mCi, preferably 0.1 to 30 mCi, more preferably 0.1 to 20 mCi. An indicated dosage range may be of from 1 to 200 μ g LIGAND labeled with 0.1 to 50 mCi, preferably 0.1 to 30 mCi, e.g. 3 to 15 mCi, γ -emitting radionuclide, depending on the γ -emitting radionuclide used. For example with In, it is preferred to use a radioactivity in the lower range, whereas with Tc, it is preferred to use a radioactivity in the upper range.

The enrichment in the tumorigenic sites with the CHELATES may be followed by the corresponding imaging techniques, e.g. using nuclear medicine imaging instrumentation, for example a scanner, γ -camera, rotating γ -camera, each preferably computer assisted; PET-scanner (Positron emission tomography); MRI equipment or CAT scanning equipment.

The CHELATES OF THE INVENTION, e.g. a major part of the γ -emitting CHELATES is substantially excreted through the kidneys and does not significantly accumulate in the liver.

CHELATES OF THE INVENTION for use in in vivo treatment are the CHELATES complexed with a α - or β -radionuclide as defined above.

Dosages employed in practising the therapeutic method of the present invention will of course vary depending e.g. on the particular condition to be treated, for example the volume of the tumor, the particular CHELATE employed, for example the half-life of the CHELATE in the tumor, and the therapy desired. In general, the dose is calculated on the basis of radioactivity distribution to each organ and on observed target uptake. For example the CHELATE may be administered at a daily dosage range having a radioactivity of from 0.1 to 3mCi/kg body weight, e.g. 1 to 3 mCi, preferably 1 to 1.5 mCi/kg body weight. An indicated daily dosage range is of from 1 to 200 μ g LIGAND labeled with 0.1 to

3 mCi/kg body weight, e.g. 0.1 to 1.5 mCi/kg body weight α - or β -emitting radionuclide, conveniently administered in divided doses up to 4 times a day.

The α - or β -emitting CHELATES OF THE INVENTION may be administered by any conventional route, in particular parenterally, e.g. in the form of injectable solutions or suspensions. They may also be administered advantageously by infusion, e.g. an infusion of 30 to 60 min. Depending on the site of the tumor, they may be administered as close as possible to the tumor site, e.g. by means of a catheter. The mode of administration selected may depend on the dissociation rate of the CHELATE used and the excretion rate.

The CHELATES OF THE INVENTION may be administered in free form or in pharmaceutically acceptable form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

The CHELATES OF THE INVENTION for use in in vivo imaging or therapy may preferably be prepared shortly before the administration to a subject, i.e. the radiolabeling with the desired detectable metal ion, particularly the desired α -, β - or γ -radionuclide, may be performed shortly before the administration.

The CHELATES OF THE INVENTION may be suitable for imaging or treating tumors such as pituitary, gastroenteropancreatic, central nervous system, breast, prostatic, ovarian or colonic tumors, small cell lung cancer, paragangliomas, neuroblastomas, pheochromocytomas, medullary thyroid carcinomas, myelomas, etc. and metastases thereof.

According to a further embodiment of the invention, the γ -emitting CHELATES OF THE INVENTION may also be used as imaging agent for the evaluation of the kidney function.

Groups of five mice are used. Each mouse is injected intravenously through a tail vein with 0.1 ml containing 1 mCi of a CHELATE OF THE INVENTION. The mice are then placed in metabolic cages for the collection of excreted urine. At 10 or 120 min. post-injection, the urethras are ligated and the mice anesthetized with chloroform. Imaging of the uropoietic system is carried out using the usual imaging technique. In this test, the γ -emitting CHELATES OF THE INVENTION improves imaging of renal excretion when administered at a dosage of from 0.1 to 30 mCi.

According to a further aspect of the invention, there is provided:

- i. a pharmaceutical composition comprising a LIGAND OF THE INVENTION in free or in pharmaceutically acceptable salt form, together with one or more pharmaceutically acceptable carriers or diluents therefor;
- ii. a pharmaceutical composition comprising a CHELATE according to the invention in free or in pharmaceutically acceptable salt form, together with one or more pharmaceutically acceptable carriers or diluents therefor.

Such compositions may be manufactured in conventional manner.

A composition according to the invention may also be presented in separate package with instructions for mixing the LIGAND with the metal ion and for the administration of the resulting CHELATE. It may also be presented in twin-pack form, that is, as a single package containing separate unit dosages of the LIGAND and the detectable metal ion with instructions for mixing them and for administration of the CHELATE. A diluent or carrier may be present in the unit dosage forms.

In the following examples, all temperatures are in ° C and $[\alpha]^{20}_D$ values uncorrected. The following abbreviations are employed:

Boc tert.-butoxycarbonyl
TFA trifluoroacetic acid
DTPA diethylenetriamine-pentaacetic acid

EXAMPLE 1: DTPA-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol

1.1 g of DPhe-Cys-Phe-DTrp-Lys(ϵ -Boc)-Thr-Cys-Thr-ol in free base (1 mM), are dissolved in 5 l of dioxan/H₂O 1/1 (v/v) and reacted with 5 g NaHCO₃. The 520 mg of DTPA dianhydride is slowly added with stirring. The reaction mixture is stirred for a further 30 min and dry-frozen. The residue is dissolved in 250 ml water and the pH is adjusted to pH 2.5 with concentrated HCl. The precipitated product is filtered out, washed and dried over phosphorus pentoxide. After chromatography on a silica-gel column, the following products are isolated: 230 mg of DTPA-DPhe-Cys-Phe-DTrp-Lys(ϵ -Boc)-Thr-Cys-Thr-ol and 500 mg of the corresponding dimer DTPA-(DPhe-Cys-Phe-DTrp-Lys(ϵ -Boc)-Thr-Cys-Thr-ol)₂.

3 ml of TFA are mixed with 200 mg of DTPA-DPhe-Cys-Phe-DTrp-Lys(ϵ -Boc)-Thr-Cys-Thr-ol. After 5 min at room temperature, the mixture is precipitated with diisopropylether, filtered out and dried. The residue is desalted over Duolite and lyophilised to yield 150 mg of the title compound:

$$[\alpha]_D^{20} = -26,6^\circ \quad (c = 1.95\% \text{ AcOH}).$$

The starting material may be produced as follows:

a) H-DPhe-Cys-Phe-DTrp-Lys(Boc)-Thr-Cys-Thr-ol

2.25 g of di-tert.butyl-pyrocabonate, dissolved in 30 ml of DMF, are slowly added in drops at room temperature to a solution of 10 g of H-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol-acetate in 100 ml of DMF. After two hours at room tempe-

perature, the solvent is drawn off under vacuum, and 200 ml of diisopropylether are added to the residue. The deposit which is being formed is filtered off, washed with diisopropylether and dried. The crude product is purified by chromatography over silica gel (eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1) and is then isolated as a white amorphous powder.

$[\alpha]_D^{20} = 29.8^\circ$ ($c = 1.28$ in DMF).

EXAMPLE 2: $\text{DTPA}-(\text{DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol})_2$

The fraction containing the intermediate product $\text{DTPA-DPhe-Cys-Phe-DTrp-Lys}(\epsilon\text{-Boc})\text{-Thr-Cys-Thr-ol})_2$ as obtained in example 1 is treated as described above for the corresponding monomeric form, the Boc protecting groups being removed to yield the title compound:

$[\alpha]_D^{20} = -24,5^\circ$ ($c = 0,55$ 95 % AcOH).

EXAMPLE 3: $\text{H}_2\text{N}-(\text{CH}_2)_5\text{-CO-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol}$

- a. 0.56 g of $\text{H-DPhe-Cys-Phe-DTrp-Lys(BOC)-Thr-Cys-Thr-ol}$, 0.5 mmole of Fmoc- ϵ -aminocaproic acid and 115 mg of hydroxybenzotriazole are dissolved in 10 ml of DMF and cooled to -30°C . To this solution is added a solution of 115 mg of dicyclohexylcarbodiimide in 5 ml of DMF (cooled to -10°C).

After a reaction time of 24 hours, during which the mixture warms to the room temperature, the resulting dicyclohexylurea is filtered off and the filtrate is diluted with water to ten times its volume. The precipitated reaction product is filtered off, washed and dried over phosphorus pentoxide. The crude product is used without further purification for the

next step.

b. Fmoc-cleavage

0.5 g of crude product from coupling reaction (a) are treated for 10 minutes at room temperature with 5 ml of DMF/piperidine 4/1 v/v (clear solution) and subsequently mixed with 100 ml of diisopropylether. The reaction product which is thus precipitated is filtered off, washed and dried. This crude product is used without further purification in the next step.

c. BOC cleavage

300 mg of crude product obtained in (1.b) are treated for 5 minutes at room temperature with 5 ml of 100 % TFA (completely dissolved) and subsequently mixed with 50 ml of diisopropylether. After addition of 2 ml of HCl/diethylether, the resulting deposit is filtered off, washed and dried in a high vacuum.

The end product is purified by chromatography on silica gel ($\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}/\text{AcOH}$ 7/3/0.5/0.5), with subsequent de-salting over Duolite (gradient: $\text{H}_2\text{O}/\text{AcOH}$ 95/5)--- $\text{H}_2\text{O}/\text{dioxane}/\text{AcOH}$ 45/50/5).

The title compound is obtained as an acetate (white lyophilisate).

$$[\alpha]_D^{20} = - 32^\circ \quad (c = 0.5 \quad 95\% \text{ AcOH}).$$

The resulting compound may be used for reaction with DTPA in accordance with the procedure of Examples 1 and 2.

EXAMPLE 4:

By following the procedure disclosed in Examples 1 and 3, the following LIGAND can be prepared:

DTPA-βAla-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol.

$[\alpha]_D^{20} = -14,8^\circ$ (c = 0.5 95 % AcOH).

EXAMPLE 5: ^{111}In labeled DTPA-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol

1 mg DTPA-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol is dissolved in 5 ml 0.01M acetic acid. The resulting solution is passed through a 0.22μ Millex®-GV filter (Registered Trade Mark) and dispensed in 0.1 ml portions and stored at -20°C. $^{111}\text{InCl}_3$ (Amersham, 1 mCi/100 μl) is prediluted in an equal volume of 0.5M sodium acetate and labeling is carried out by mixing the ligand with the InCl_3 solution and gentle homogenisation at room temperature.

HEPES buffer, pH 7.4, is then added to make a solution 10^{-6} M.

EXAMPLE 6: ^{90}Y labeled DTPA-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol

^{90}Y is obtained from a ^{90}Sr - ^{90}Y radionuclide generator. The construction of the generator, its elution and the conversion of the [^{90}Y]EDTA to the acetate complex are performed in accordance with the method disclosed by M.Chinol and D.J. Hnatowich in J. Nucl.

Med. 28, 1465-1470 (1987). 1 mg of DTPA-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol dissolved in 5ml 0.01M acetic acid is allowed to warm to room temperature and 1.0 mCi of ^{90}Y in 50 μl sterile 0.5M acetate is added. The mixture is then left undisturbed for 30 min to 1 hr to maximize chelation.

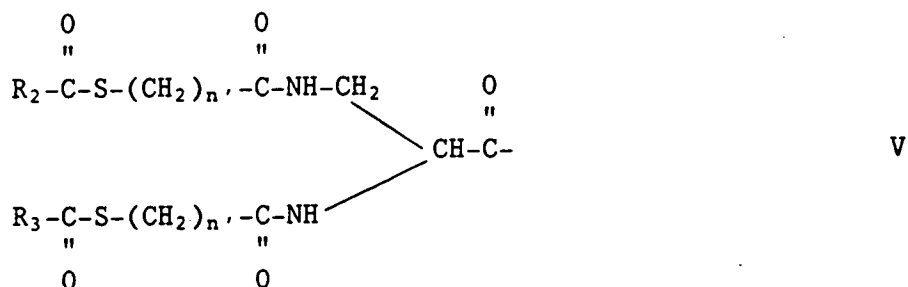
One group of somatostatin peptides of the invention are e.g. somatostatin analogues, which contain at least on one of the amino acid units a chelating group which is attached to said amino group by an amide bond, the chelating group being other than a sugar residue, in free form or in salt form.

One group of CHELATES OF THE INVENTION are the somatostatin peptides just mentioned above complexed with a detectable element, e.g. a metal ion, in free form or in salt form.

CLAIMS

1. A somatostatin peptide bearing at least one chelating group capable of complexing an element detectable by therapeutic or in vivo diagnostic techniques, the chelating group being covalently linked to an amino group of said peptide, this amino group having no significant binding affinity for somatostatin receptors, the thus modified somatostatin peptide having binding affinity for somatostatin receptors, and the chelating group being other than a sugar residue, in free form or in salt form.
2. A somatostatin peptide bearing at least one chelating group complexed with an element detectable by therapeutic or in vivo diagnostic techniques, the chelating group being covalently linked to an amino group of said peptide and this amino group having no significant binding affinity for somatostatin receptors, the thus modified somatostatin peptide having binding affinity for somatostatin receptors, in free form or in salt form.
3. A somatostatin peptide according to claim 1 or 2, wherein the chelating group is attached to the terminal amino group of the somatostatin peptide.
4. A somatostatin peptide according to any one of the preceding claims, wherein the chelating group is attached directly or indirectly to the amino group of said peptide.
5. A somatostatin peptide according to any one of the preceding claims, wherein the chelating group is attached by an amide bond to said peptide.

- $$\begin{array}{c} \text{O} \qquad \qquad \text{O} \qquad \qquad \text{O} \\ \parallel \qquad \qquad \parallel \qquad \qquad \parallel \\ \text{R}_1-\text{C}-\text{S}-(\text{CH}_2)_n-\text{C}-(\text{TT})_i-\text{C}- \end{array} \quad \text{IV}$$

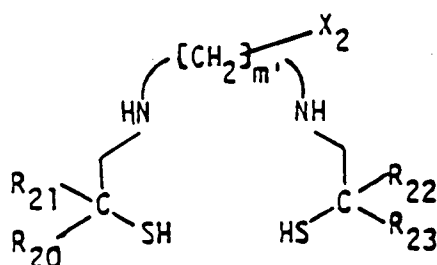


each of R₁, R₂ and R₃ independently is C₁₋₆alkyl, C₆₋₈aryl or C₇₋₉arylalkyl, each optionally substituted by OH, C₁₋₄alkoxy, COOH or SO₃H,

i is an integer from 2 to 6, and

groups derived from bis-aminothiol derivatives, from dithia-semicarbazone derivatives, from propylene amine oxime derivatives, from diamide dimercaptides or from porphyrins, in free form or in salt form.

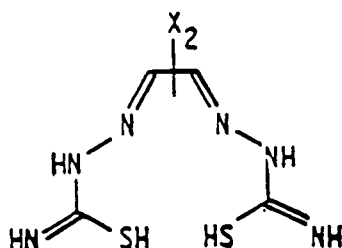
7. A somatostatin peptide according to claim 6, wherein the chelating group is derived from a compound of formula VI



VI

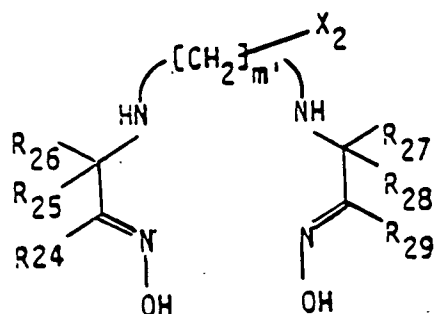
wherein
each of R_{20} , R_{21} , R_{22} and R_{23} independently is hydrogen or C_{1-4} alkyl,
 X_2 is a group capable of reacting with the N-amino group of the peptide, and
 m' is 2 or 3,

from a compound of formula VII



VII

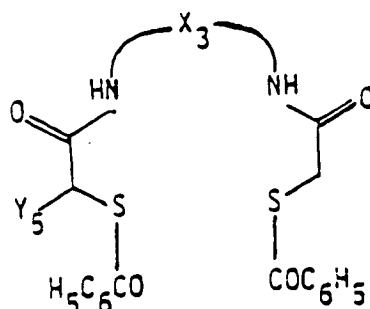
wherein X_2 is as defined above,
from a compound of formula VIII



VIII

wherein

each of R_{24} , R_{25} , R_{26} , R_{27} , R_{28} and R_{29} independently are hydrogen or C_{1-4} alkyl, and X_2 and m' are as defined above, or from a compound of formula IX



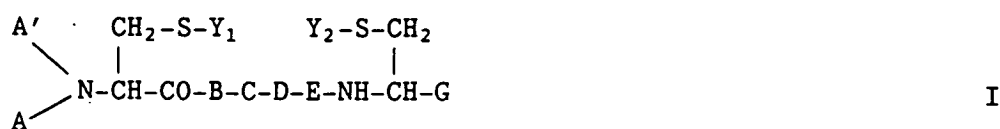
IX

wherein

X_3 is a divalent radical optionally substituted and bearing a group capable of reacting with the N-amino group of the peptide, and Y_5 is H or CO_2R_{30} wherein R_{30} is C_{1-4} alkyl.

8. A somatostatin peptide according to claim 6, wherein the chelating group is derived from ethylene diaminetetraacetic acid (EDTA), diethylene triamine pentaacetic acid (DTPA), ethylene glycol-0,0'-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED), triethylenetetramine hexaacetic acid (TTHA), substituted EDTA or -DTPA 1,4,7,10-tetra-azacyclodecane-N,N',N'',N'''-tetraacetic acid (DOTA) and 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), in free form or in salt form.

9. A somatostatin peptide according to claim 8, wherein the chelating group is derived from diethylene triamine penta-acetic acid (DTPA), in free form or in salt form.
10. A somatostatin peptide according to any one of the preceding claims, wherein the somatostatin peptide is derived from a compound of formula I



wherein

A is C₁₋₁₂alkyl, C₇₋₁₀phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C₁₋₁₁alkyl, phenyl or C₇₋₁₀-phenylalkyl, or

ii) RCO- is

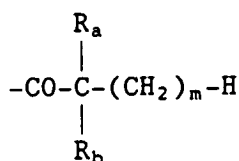
a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO₂, NH₂, OH, C₁₋₃alkyl and/or C₁₋₃alkoxy;

b) the residue of a natural α-amino acid other than defined under a) above, naphthyl-methyl or pyridyl-methyl or a residue of a corresponding D-amino acid, or

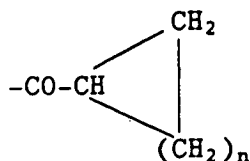
- c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

the α -amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- C_{1-12} alkylated or substituted by C_{1-8} alkanoyl,

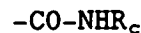
A' is hydrogen, C_{1-12} alkyl or C_{7-10} phenylalkyl,
 Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of formulae (1) to (5)



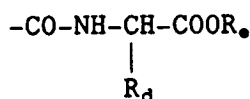
(1)



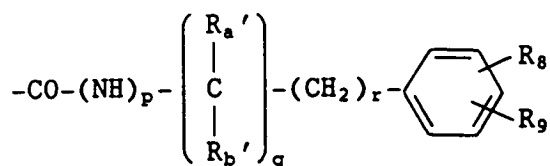
(2)



(3)



(4)



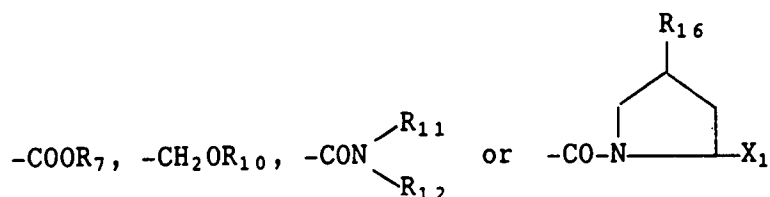
(5)

wherein

- R_a is methyl or ethyl
 R_b is hydrogen, methyl or ethyl
 m is a whole number from 1 to 4
 n is a whole number from 1 to 5

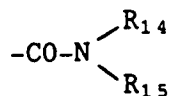
- R_c is (C₁₋₆)alkyl
- R_d represents the substituent attached to the
α-carbon atom of a natural α-amino acid
(including hydrogen)
- R_e is (C₁₋₅)alkyl
- R_a' and R_b' are independently hydrogen, methyl or ethyl,
- R₈ and R₉ are independently hydrogen, halogen, (C₁₋₃)alkyl
or (C₁₋₃)alkoxy,
- p is 0 or 1,
- q is 0 or 1, and
- r is 0, 1 or 2,
- B is optionally by halogen, NO₂, NH₂, OH,
C₁₋₃alkyl and/or C₁₋₃alkoxy ring-substituted Phe
(including pentafluorophenylalanine), or
β-naphthyl-Ala
- C is (L)-Trp- or (D)-Trp- optionally α-N-methyl-
ated and optionally benzene-ring-substituted by
halogen, NO₂, NH₂, OH, C₁₋₃alkyl and/or C₁₋₃
alkoxy,
- D is Lys, Lys in which the side chain contains O
or S in β-position, γF-Lys or δF-Lys, optionally
α-N-methylated, or a 4-aminocyclohexylAla or
4-aminocyclohexylGly residue
- E is Thr, Ser, Val, Phe, Ile or an aminoisobutyric
or aminobutyric acid residue

G is a group of formula



wherein

- R_7 is hydrogen or C_{1-3} alkyl,
 R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R_{11} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenyl-alkyl,
 R_{12} is hydrogen, C_{1-3} alkyl or a group of formula $-\text{CH}(\text{R}_{13})-\text{X}_1$,
 R_{13} is CH_2OH , $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, or $-\text{CH}(\text{CH}_3)\text{OH}$ or represents the substituent attached to the α -carbon atom of a natural α -amino acid (including hydrogen), butyl or naphthyl-methyl, and
 X_1 is a group of formula $-\text{COOR}_7$, $-\text{CH}_2\text{OR}_{10}$ or



wherein

- R_7 and R_{10} have the meanings given above,
 R_{14} is hydrogen or C_{1-3} alkyl and
 R_{15} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenyl-alkyl, and
 R_{16} is hydrogen or hydroxy,

with the proviso that

when R_{12} is $-\text{CH}(\text{R}_{13})-\text{X}_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2-and 7-position and any residues Y₁ 4) and Y₂ 4) each independently have the (L)- or (D)- configuration in free form or in salt form.

11. A somatostatin peptide according to claim 10, wherein in formula I A is RCO and A' is hydrogen.
12. A somatostatin peptide according to claim 10 or 11, wherein in formula I

G is -CO-NH-CH(R₁₃)-X₁

wherein R₁₃ is -CH₂OH, -CH(CH₃)-OH, -(CH₂)₂-OH, -(CH₂)₃-OH, isobutyl or butyl, and

X₁ is -CO-NR₁₄R₁₅ or -CH₂OR₁₀ wherein R₁₀, R₁₄ and R₁₅ are as defined in claim 10.

13. A somatostatin peptide according to any one of the preceding claims, wherein the somatostatin peptide is derived from

H-(D)Phe-Cys-Phe-(D)Trp-Lys-Thr-Cys-Thr-ol

also known as octreotide.

14. A somatostatin peptide according to any one of claims 1 to 13, wherein the chelating group is attached to said peptide through a spacer group of formula α_1

Z-R₃₅-CO-

(α_1)

wherein

R₃₅ is C₁₋₁₁alkylene, C₂₋₁₁alkenylene or -CH(R')- wherein R' is the residue attached in α to a natural α -amino acid, and

2 is a functional moiety capable of covalently reacting with the chelating agent.

15. A somatostatin peptide bearing a chelating group, which is


DTPA-(D)Phe-Cys-Phe-(D)Trp-Lys-Thr-Cys-Thr-ol
in free form or in salt form,

the chelating group DTPA being covalently linked to the terminal amino group of said peptide, this amino group having no significant binding affinity for somatostatin receptors, the thus modified somatostatin peptide having binding affinity for somatostatin receptors.

16. A somatostatin peptide according to any one of claims 2 to 14, wherein the detectable element is a γ -emitting radionuclide.

17. A somatostatin peptide according to claim 16, wherein the detectable element is ^{111}In or $^{99\text{m}}\text{Tc}$.

18. A somatostatin peptide bearing a chelating group in complexed form, which is


 ^{111}In labelled DTPA-(D)Phe-Cys-Phe-(D)Trp-Lys-Thr-Cys-Thr-ol,
in free form or in pharmaceutically acceptable salt form,

the chelating group DTPA being covalently linked to the terminal amino group of said peptide and this amino group having no significant binding affinity for somatostatin receptors,
the thus modified somatostatin peptide having binding affinity for somatostatin receptors.

19. A somatostatin peptide according to any one of claims 2 to 14, wherein the detectable element is an α - or β -emitting radionuclide.
20. A somatostatin peptide according to claim 19, wherein the detectable element is ^{90}Y .
21. A somatostatin peptide bearing a chelating group, which is ^{90}Y labelled $\text{DTPA}-(\text{D})\text{Phe}-\text{Cys}-\text{Phe}-(\text{D})\text{Trp}-\text{Lys}-\text{Thr}-\text{Cys}-\text{Thr}-\text{ol}$,
in free form or in pharmaceutically acceptable salt form,

the chelating group DTPA being covalently linked to the terminal amino group of said peptide and this amino group having no significant binding affinity for somatostatin receptors,
the thus modified somatostatin peptide having binding affinity for somatostatin receptors.
22. A somatostatin peptide according to any one of claims 2 to 14 and 16 to 21, in free form or in pharmaceutically acceptable salt form for use as a pharmaceutical.
23. A somatostatin peptide according to any one of claims 16 to 18, in free form or in pharmaceutically acceptable salt form for use as an imaging agent of somatostatin receptor positive tumors or metastases.
24. A somatostatin peptide according to any one of claims 19 to 21, in free form or in pharmaceutically acceptable salt form for use in radiotherapy of somatostatin receptor positive tumors or metastases.

25. A pharmaceutical composition comprising a somatostatin peptide according to any one of claims 1 to 24, in free form or in pharmaceutically acceptable salt form in association with a pharmaceutically carrier or diluent.
 26. A somatostatin peptide according to claim 1 with reference to any one of Examples 1 to 4.
 27. A somatostatin peptide according to claim 2 with reference to Example 5 or 6.
 28. A package containing separate unit dosages of a somatostatin peptide according to any one of claims 1 to 15 and of a detectable element to be mixed together before use as imaging agent or therapeutic agent.
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